DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE TABLETS OF ROPINIROLE USING VARIOUS POLYMERS

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IN

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Submitted by
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The dissertation or any part thereof has not been submitted elsewhere for any other degree, diploma or fellowship or any other titles.

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DECLARATION

I hereby declare that the dissertation work entitled "**DEVOLOPMENT AND EVALUATION OF EXTENDED REALEASE TABLET OF ROPINIROLE**" is based on original work carried out by the in **Annai Veilankanni's pharmacy College, Saidapet, Chennai** and formulation at **M\s.KEMWELL BIOPHARMA PVT LTD, BANGALORE** under the guidance of **Mr.S.Manjunatha, Head Research & Development** for submission to The Tamil Nadu Dr.M.G.R.Medical University in the partial fulfillment of the requirement for the award of Degree Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge.

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ABBREVATIONS

% RSD	Percentage Relative Standard Deviation
% v/v	Percentage volume/volume
%	Percentage
λ	Lambda
µg	Microgram
λ_{max}	Absorption maximum
µ	Micron
AUC	Area under the curve
HCl	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
IP	Indian Pharmacopoeia
LOD	Limit of Detection
LOQ	Limit of Quantitation
mg	Milligram
ml	Milliliter
mM	Millimole
ng	Nonogram
nm	Nanometer

r	Regression coefficient
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
S.D	Standard Deviation
S.E	Standard Error
USP	United States Pharmacopoeia
U.S.DEA	United States Drug Enforcement Administration
UV	Ultraviolet
EZP	Eszopiclone (Drug)

Introduction

INTRODUCTION

An ultimate goal of any dosage regimen in the drug therapy of any disease is one which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at a particular frequency. The frequency of administration or the dosing interval of any drug depends upon its half life or mean residence time (MRT) and its therapeutic index. Extended and controlled release represents separate drug delivery processes. Extended release (ER) constitutes any dosage form that provides medication over extended period of time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this can be of temporal nature, spatial nature or both. In other words, the system attempts to control drug concentration in the target tissue. Thus there are sustained release systems that cannot be considered controlled drug delivery systems. The goal of ER[1] dosage form is to maintain therapeutic blood or tissue levels of the drug for extended period which try to mimic zero-order drug release. Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastro intestinal disturbances.

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally

recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology[2] is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release, sustained release delivery systems are constantly being developed and tested.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

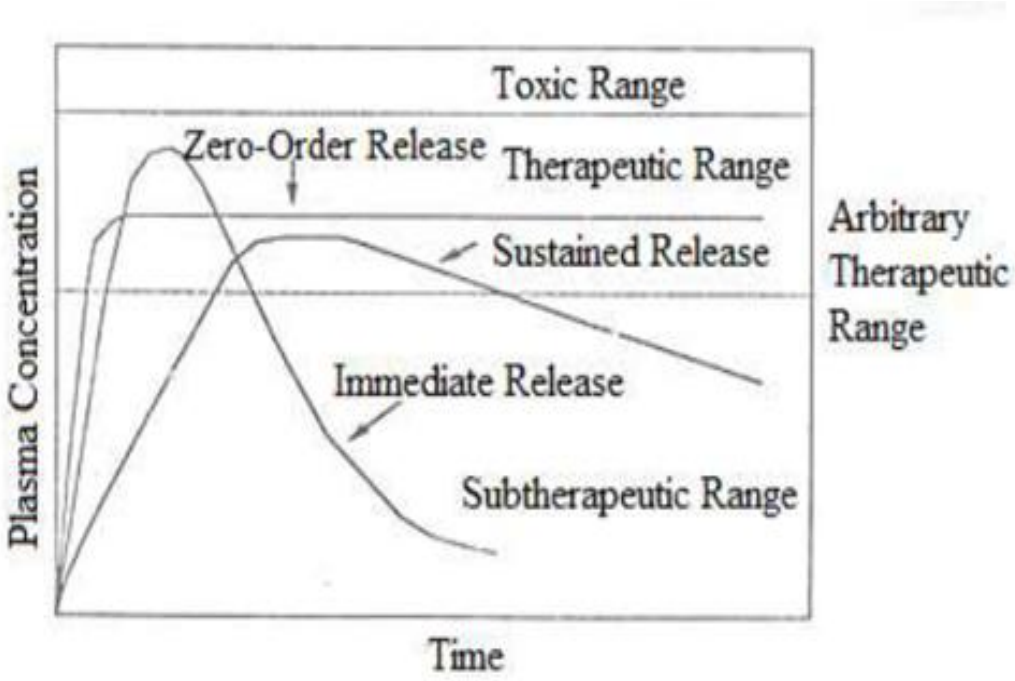


Fig.1.Plasma concentration-time profile

Advantages of Extended release dosage forms [3]

- Reduction in dosing frequency.
- Reduced fluctuations in circulating drug levels.
- Increased patient compliance.
- Extended release allows for sustained therapeutic blood levels of the drug.
- Sustained blood levels provide for a prolonged and consistent clinical response in the patient.

- Economic benefit.
- Minimize toxicity, decrease adverse reactions.
- Drugs with very short elimination half-lives, an extended-release drug product maintains the efficacy over a longer duration.

Disadvantages of extended release dosage forms

- Dose dumping.
- Reduced potential for dosage adjustment.
- Poor systemic availability in general.
- If the patient suffers from an adverse drug reaction or accidentally becomes intoxicated the removal of drug from the system is more difficult with an extended release drug product.
- Orally administered extended-release drug products may yield erratic or variable drug absorption as a result of various drug interactions with the contents of the GI tract and changes in the GI motility.

Modified release drug product[4-5]

The term modified release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance.

Types of Modified release drug products

- **Extended release dosage forms:**A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form.

  Ex: Controlled release, Sustained release.

Sustained release: It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a pre-determined rate.

Controlled release: It includes any drug delivery system from which the drug is delivered at a predetermined rate over a long period.

- **Delayed release dosage forms:** A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration.

  Ex: Enteric coated dosage forms.

- **Targeted release dosage forms**:A dosage forms that releases drug at /near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics.

Design of Extended release products

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspension have been recently introduced. The classifications of such systems are as follows:

- Diffusion controlled systems.
- Dissolution controlled systems.
- Dissolution and Diffusion controlled systems.
- Osmotically controlled systems.
- Ion exchange systems.

Diffusion controlled systems[6]

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer.

Ingeneral two types of sub classes of diffusion systems are recognized they are

a. Réservoir devises.

b. Matrix devises.

a. Reservoir devices

Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system.

The process of diffusion is generally described by Ficks equations,

$$J = D\frac{dc}{dx}$$

Where, J = Flux (amount/area –time)

D = Diffusion co-efficient of drug in the membrane (area/time)

dc/dx= rate of exchange in concentration C, with respect to a distance X in the membrane.

b. Matrix devices

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi.

$\frac{dm}{dh} = C_0 d_h - \frac{Cs}{2}$.

Where, dm = Change in the amount of drug released per unit area.

d_h= Change in the thickness of the zone of matrix that have been depleted of drug.

Co = Total amount of drug in unit volume of matrix.

Cs =Saturated concentration of drug within the matrix.

Dissolution controlled systems[7]

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution. This being the case, SR preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

The dissolution process at steady state is described by Noyes-Whitney equation.

$\frac{dc}{dt} = KDA(Cs - C) = \frac{DA(Cs-C)}{h}$

Where,dc/dt = Dissolution rate

Ko = Diffusion co-efficient

Cs = Saturation solubility of the solid

C = Concentration of solute in bulk solution.

h = Thickness of diffusion layer.

Dissolution and diffusion controlled release system

Strictly speaking, therapeutic systems will never be dependent on dissolution only or diffusion only. In practice, the dominant mechanism for release will over

shadow other processes enough to allow classification as either dissolution rate limited or diffusion controlled.

Osmotically controlled systems

This device is fabricated as tablet that contains water soluble osmotically active drug, of that was blended with osmotically active diluents by coating the tablet with a cellulose triacetate barrier which functions as a semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane.

Ion exchange Systems

These are salts of cationic or anionic exchange resins or insoluble complexes in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

Factors affecting Extended release dosage forms[8]

Dose Size

If an oral product has a dose size greater that 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

Aqueous Solubility

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism.

The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate

Partition coefficient

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability.

pka

It is the relationship between pka of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form

Drug stability

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation

Molecular size and diffusivity

The ability of drug to diffuse through membranes its so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight).Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10^{-8} to 10^{-9} cm^2 / sec. with values on the order of 10^{-8} being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm^2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

Biological half Life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release

is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

Metabolism

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic. Process device a specific period, allowing more complete conversion of the drug to its metabolite.

Mechanism of drug release

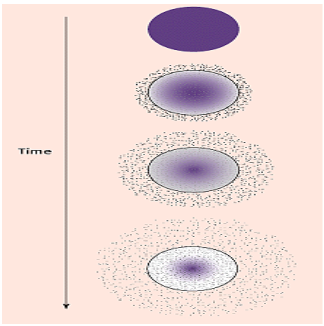


Fig.2. Drug delivery from a typical matrix drug delivery system.

Polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

Ideal candidates for Extended release drug delivery[9]

- Molecular weight: <1000mg
- Solubility: 0.1 mcg/ml
- $_{p}$ka: >0.1% to 1% at pH 1 to 7.8
- Apparent partition coefficient: 0.5 to 2
- Stability: stable in GI environment
- Release: Release should not be influenced by pH and enzymes
- Elimination Half Life; Preferably between 0.5 and 8hrs
- Total clearance: Extensively metabolised by the liver provided the rate of metabolism is slow.
- Intrinsic Absorption rate constant: Drug is absorbed rapidly
- Therapeutic range: wide

Unsuitable candidate for extended release dosage forms[10]

- Shorter $t_{1/2}$
- Longer $t_{1/2}$
- Narrow Therapeutic index
- Large dose
- Not absorbed rapidly

Literature Review

LITERATURE REVIEW

Shahrzad *et al.*,Explained that Hypromellose (hydroxypropyl methylcellulose, HPMC) matrices are widely used in the formulation of sustained release dosage forms. The integrity and performance of an HPMC matrix formulation depends on rapid hydration and gel formation upon ingestion. Due to the recent alert issued by the Food and Drug Administration regarding the potential negative influence of alcoholic beverages on extended release (ER) formulations, several researchers have evaluated the potential influence of hydro alcoholic media on drug release from ER dosage forms. It has been reported that HPMC matrix formulations do not show "dose dumping" in hydro alcoholic media. The purpose of this study was a fundamental investigation on the effect of hydro alcoholic solutions (0–40% v/v ethanol) on textural and rheological properties of different viscosity grades of neat HPMC, as the functional ingredient within a hydrophilic matrix. In general, hydro alcoholic solutions had little effect on gel formation and mechanical properties of hydrated compacts, while the rheological behaviour of HPMC showed dependency on the ethanol content of such solutions.

Amelia Avachat *et al.*,Employedan emulsion solvent evaporation method to prepare microspheres of ropinirole hydrochloride, a highly water soluble drug, by using ethyl cellulose and PEG with the help of 32 full factorial design. The microspheres were made by incorporating the drug in a polar organic solvent, which was emulsified using liquid paraffin as an external oil phase. Effects of various process parameters such as viscosity of the external phase, selection of the internal phase, surfactant selection and selection of stirring speed were studied. Microspheres were evaluated for product yield, encapsulation efficiency and particle size. Various

drug/ethyl cellulose ratios and PEG concentrations were assayed. *In vitro* dissolution profiles showed that ethyl cellulose microspheres were able to control release of the drug for a period of 12 h.

Juliane Weber*et al.,* developed Two well designed, placebo- or active comparator-controlled trials examined the efficacy of ropinirole prolonged release in patients with advanced Parkinson's disease sub optimally controlled by levodopa. In the placebo-controlled trial, 24 weeks' therapy with ropinirole prolonged release 6–24 mg once daily reduced hours of 'off' time (primary endpoint) to a significantly greater extent than placebo. In active comparator-controlled trial, significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients maintained at 20% reduction from baseline in 'off' time at plasma concentration week 24 (primary endpoint). This article focuses solely on the relative bioavailability of the prolonged- and immediate adjunct to levodopa in patients with advanced Parkinsons disease.

R. Pahwa *et al.,* Evaluated the efficacy of ropinirole 24-hour prolonged release (ropinirole 24-hour) as an adjunct to levodopa in patients with Parkinson disease (PD) and motor fluctuations. *Methods:* In a double-blind, placebo-controlled, 24-week study, 393 subjects with PD were randomized to ropinirole 24-hour (n _ 202) or placebo (n _ 191). The primary outcome measure was reduction in hours of daily "off " time. *Results:* At week 24, the mean dose of ropinirole 24-hour was 18.8 mg/day with a mean reduction in daily levodopa of 278 mg. There was a mean reduction in daily "off " time of 2.1 hours in the ropinirole 24-hour group and 0.3 hours with placebo. Secondary outcome measures including change in hours and percent of daily "on" time and "on" time without troublesome dyskinesia, Unified PD Rating Scale motor and activities of daily living subscales, Beck Depression

Inventory-II, PDQ-39 subscales of mobility, activities of daily living, emotional well-being, stigma and communication, and PD Sleep Scale were significantly improved at week 24 with ropinirole 24-hour. The most common adverse events (AE) with ropinirole 24-hour were dyskinesia, nausea, dizziness, somnolence, hallucinations, and orthostatic hypotension and AEs led to study withdrawal in 5% of both the active and placebo groups.

J. Goole *et al.,* Studied the scintigraphic and pharmacokinetic studies were conducted on 10 healthy, fed volunteers. Two concepts of sustained-release floating minitablets – Levo-Form 1 (matrix) and 2 (coated) –were evaluated and compared to the marketed product Prolopa® HBS 125. All the floating forms were radio labelled with 111In in order to evaluate their gastric residence time using _-scintigraphy. It was shown that the three formulations offered almost the same mean gastric residence time, which was about 240 min. Prolopa® HBS 125 and Levo-Form 2 presented intragastric disintegration, which can lead to a more pronounced "peak & valley" effect on the plasma concentration–time profile of levodopa. In contrast, the plasma concentration–time profile of levodopa following the administration of Levo-Form 1 was more evenly distributed. Moreover, Levo-Form 1 provided the lowest variations between men and women in terms of AUC and *C*max values. Finally, when the same amount of inhibitors of extra cerebral dopa decarboxylase – carbidopa and benserazide – had been administrated, the mean AUC, *C*max and *T*max values obtained for benserazide were lower than those obtained for carbidopa.

Ranjith Kumar *et al.,*reviewed that oral drug delivery remains the most preferred option for administration for various drugs. Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral Sustained release (S.R) / Controlled

release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutic, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. This review describes the various factors influencing the design and performance of sustained/controlled release products along with suitable illustrations.

Peter Lewitt*et al.,*described that Levodopa serves as the gold standard of anti-parkinsonian therapy and nearly every patient with Parkinson's disease eventually receives this drug. To improve upon levodopa therapy, several forms of treatment have been devised to augment its actions, and new delivery systems are under development. This new research offers promise for improving outcomes with this highly effective therapy.

Viness Pillay *et al.,*explained that Parkinson's disease (PD) affects one in every 100 persons above the age of 65 years, making it the second most common neurodegenerative disease after Alzheimer's disease. PD is a disease of the central nervous system that leads to severe difficulties with body motions. The currently available therapies aim to improve the functional capacity of the patient for as long as possible; however they do not modify the progression of the neurodegenerative process. The need for newer and more effective agents is consequently receiving a great deal of attention and consequently being subjected to extensive research. This review concisely compiles the limitations of currently available therapies and the most recent research regarding neuroprotective agents, antioxidants, stem cell

research, vaccines and various surgical techniques available and being developed for the management of PD.

Vincenzo Bonifati *et al.,*reviewed that Levodopa remains the most effective drug for Parkinson's disease (PD). However, its benefits are limited owing to extensive metabolism by catechol-*O* -methyltransferase (COMT), especially if levodopa is used in combination with peripheral dopa decarboxylase inhibitors. A new generation of potent, orally active, selective, and reversible COMT inhibitors has become available recently. Among these, tolcapone and entacapone have been best characterised. Preclinical and clinical studies have shown that COMT inhibitors markedly enhance levodopa availability and prolong its plasma half-life. In recent large clinical trials they proved to be able to ameliorate motor fluctuations, reduce disability, and decrease levodopa requirements in Parkinson disease patients. The tolerability profiles of entacapone and tolcapone are good. COMT inhibition promises to become an important means of extending the benefits of levodopa therapy in Parkinson disease.

Adnan Azeem *et al.,* designed an effective transdermal nano-emulsion drug delivery system can however resolve these issues effectively with greater therapeutic benefits and clinical significance. Therefore, the present work focuses precisely on pharmacokinetic, biochemical and mechanistic assessment of transdermal nanoemulsion gel in rats induced with Parkinson lesioned brain by 6-OHDA. DSC and FT-IR studies showed that NEG affects the normal lipid packing of stratum corneum to enhance the drug permeation. Study of pharmacokinetic parameters (AUC, Cmax, and Tmax) revealed a greater and more extended release of ropinirole from nanoemulsion gel compared to that from a conventional gel (RPG) and oral marketed tablet (Ropitor®). The AUC0→∞ for RPCNG and RPTNG was found to

be 928.07 ± 206.5 and 1055.99 ± 251.7 ng h/mL, respectively in comparison to 137.25 ± 31.3 and 467.15 ± 106.1 ng h/mL for RPG and oral tablet, respectively. The relative bioavailability of ropinirole has been enhanced more than two fold by RPTNG. Furthermore, antiparkinson activity was evaluated in terms of estimating the level of thiobarbituric acid reactive substances, glutathione antioxidant enzymes and catalase in lesioned brain of rats. Formulations were also found to be non-toxic and non-irritant by histological investigations.

Lauren Seeberger *et al.*,explained that The bioavailability of drugs used to treat chronic diseases such as Parkinson's disease may have important implications for their clinical utility. Drugs with low bioavailability may cause a wide variation in clinical response between patients and even in the same patient. In addition, numerous factors including gender, age, and gastric motility may affect a drug's bioavailability. This is especially important in patients with Parkinson's disease, who develop response fluctuations as the disease progresses. Strategies that may improve the bioavailability of levodopa, the most efficacious medication for Parkinson's disease, include co administering levodopa with carbidopa, a decarboxylase inhibitor, or with a catechol- O-methyltransferase inhibitor or using an alternative route of administration. Other adjunctive therapies used to treat Parkinson's disease have a wide range of bioavailability, which may also affect clinical outcomes. The bioavailability of adjunctive medications may be improved by the use of alternative formulations as well, such as orally disintegrating tablets or transdermal delivery. Considering bioavailability of a medication when prescribing drugs to treat Parkinson's disease may improve patient response and minimize adverse effects.

Deepak Sahu *et al.,* developed sustained release matrix tablets of quetiapine fumarate using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and PVP K30. Varying ratios of drug and polymer like were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of two different rate controlling material. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Dissolution data was analysed by Higuchi expression. Among all the formulations, formulation QFSRT/08 which contains 60% HPMC K15M and 06% of PVP K30 release the drug which follow Higuchi kinetics via, swelling, diffusion and erosion and the release profile of formulation QFSRT/08 was comparable with the prepared batch products. Stability studies (40±2ºC/75±5%RH) for 6 months indicated that quetiapine fumarate was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.

Wakode Rajeshri *et al.,* developed Sustained release tablets of pramipexole to be taken once daily were formulated and characterized. Matrix system based on combination of different polymers like hydroxy propyl methylcellulose (HPMC), Eudragit RL 100 and ethyl cellulose in varying concentrations were studied to get the desired sustained release profile over a period of 24 h. The granules were evaluated for angle of repose, bulk density, compressibility index, and drug content. The granules showed satisfactory flow properties, compressibility and drug content. The release pattern of pramipexole was fitted to different models based on

coefficient of correlation. Formulation (F10) containing HPMC (16% w/w) and Ethyl cellulose (5.4 % w/w) gave the desired release for once a day administration. The drug release was found to be diffusion controlled coupled with erosion having high correlation for Higuchi release pattern. The release pattern was close to the theoretical release profile.

Raghavendra Rao *et al.,* has developed sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug up to 12 hrs. Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the matrix tablets. The

DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.

Yucheng Sheng *et al.,*Evaluated an understanding of dose proportionality is essential in drug development, and the results are of great clinical importance for predicting the effects of dose adjustments. However, little consensus exists with regard to study design and analysis. The aim of this paper was to produce a detailed profile of the information on dose proportionality studies in the last 10 years and to provide a foundation for reflection and debate on future priorities. A total of 147 publications comprising 156 studies were analyzed. The typical dose proportionality study enrolled 20 to 30 subjects and randomly allocated them into 3 to 4 dose levels to investigate pharmacokinetic behaviours within a dose ratio range of 2-6. The most common design was the crossover experiment (52.6%), and evaluating dose-adjusted pharmacokinetic parameters followed by hypothesis testing (43%) was the most frequent statistical approach. However, the alternative crossover design and equivalence criterion based on the power model represented only 4% and 8% of studies, respectively. The power model as a recommendable empirical relationship to assess dose proportionality was applied in 25 (16%) studies. This research suggests that the alternative crossover design and power model statistical method should be attracting more attention in order to obtain more information in studies with limited subjects.

Eytan Klausner *et al.,* reviewed levodopa has to be administered continuously to the upper parts of the intestine in order to maintain sustained therapeutic levels. This may be achieved by a controlled release (CR) gastro retentive dosage form (GRDF). The aim of this work was to develop a novel GRDF, based on unfolding polymeric membranes, that combines extended dimensions with high rigidity, and to examine

the pharmacokinetics of levodopa compounded in the GRDF. The 21 successful CR-GRDF maintained therapeutic levodopa concentrations (.500 ng ml) over 9 h. In comparison to non-gastro retentive CR-particles and oral solution, mean absorption time was significantly extended. These outcomes demonstrate that the CR-GRDF may be used to improve levodopa therapy and can be applied to extend the absorption of other narrow absorption window drugs that require continuous input.

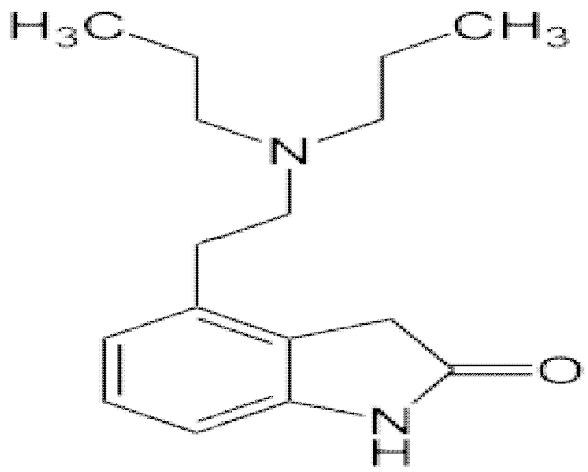
Drug Profile

DRUG PROFILE[27-30]

ROPINIROLE

IUPAC Name: 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one

Chemical structure



Molecular formula: $C_{16}H_{24}N_2O$

Molecular weight: 296.84 gm/mol

Therapeuic action

Anti-parkinsonism

Mechanism of action[28]

Ropinirole is a non-ergoline dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes.It acts on post synaptic neurons, acting selectively on Dopamine D2/D3 receptors and helps to improves motor function. It belongs to Dopaminergic agonist

Pharmacokinetcs[29]

Route: oral

Bioavailability

In clinical studies with immediate-release ropinirole, over 88% of a radiolabeled dose was recovered in urine, and the absolute bioavailability was 45% to 55%, indicating approximately 50% first-pass effect. Ropinirole displayed linear kinetics up to doses of 24 mg/day (8 mg immediate-release, 3 times a day). Relative bioavailability of REQUIP XL Extended-Release Tablets compared with immediate-release tablets was approximately 100%.

Distribution

Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg

Metabolism

Ropinirole is extensively metabolized by the liver. The major metabolic pathways are N-despropylation and hydroxylation to form the inactive N-despropyl metabolite and hydroxyl metabolites.

Elimination

Less than 10% of the administered dose is excreted as unchanged drug in urine.

Adverse reactions[29]

The following adverse reactions are observed in ropinirole include

- Falling asleep during activities of daily living
- Syncope
- Symptomatic hypotension, hypotension, postural/orthostatic hypotension
- Elevation of blood pressure and changes in heart rate

Drug interactions

Ciprofloxacin

Co administration of ciprofloxacin, an inhibitor of CYP1A2, with ropinirole increased ropinirole AUC by 84% on average and C_{max} by 60%

L-dopa

Oral administration of ropinirole increased mean steady-state C_{max} of L-dopa by 20%, but its AUC was unaffected

Estrogens

Population pharmacokinetic analysis revealed that higher doses of estrogens (usually associated with hormone replacement therapy [HRT]) reduced the oral clearance of ropinirole by approximately 35%.

Warnings and precautions[30]

- Syncope, sometimes associated with bradycardia,
- Symptomatic hypotension (including postural/orthostatic hypotension)
- Elevation of blood pressure and changes in heart rate
- Hallucination may occur
- Dyskinesia may be caused or exacerbated. Decreasing the L-dopa dose may lessen or eliminate this side effect

Dosage forms and strengths

Tablets: 2 mg, 4 mg, 6 mg, 8 mg, and 12 mg

Polymer Profile

POLYMER PROFILE

HYDROXY PROPYL METHYL CELLULOSE[31-33]

Nonproprietary Names

BP: Hypromellose, JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum, USP: Hypromellose

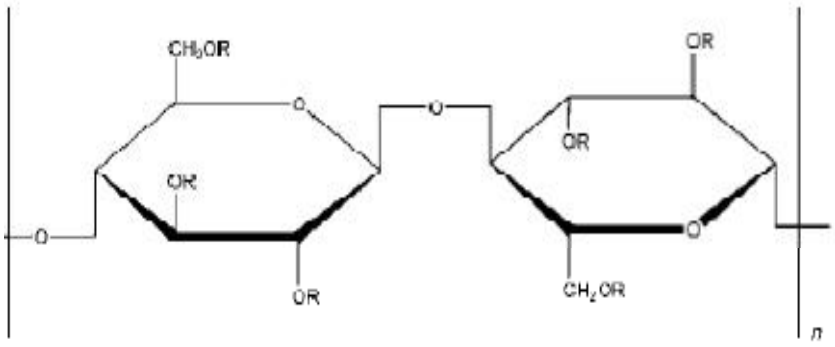
Synonyms

Hydroxyl propyl methylcellulose, HPMC; Methocel, methyl cellulose, propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly O-methylated and O-(2 hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Molecular weight is approximately 10 000–1 500 000.

Structural formula



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Description

Hypromellose is an odourless and tasteless, white or creamy white fibrous or granular powder.

Typical Properties

Density (bulk): 0.341 g/cm^{3}Melting point: Browns at 190–200^{0}CMoisture content: Hypromellose absorbs moisture from the atmosphere;

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology [33]

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an

adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products

SODIUM CARBOXY METHYL CELLULOSE

Nonproprietary Names

BP: Carmellose sodium,JP: Carmellose sodium,

PhEur: Carmellosum natricum, USP: Carboxymethylcellulose sodium

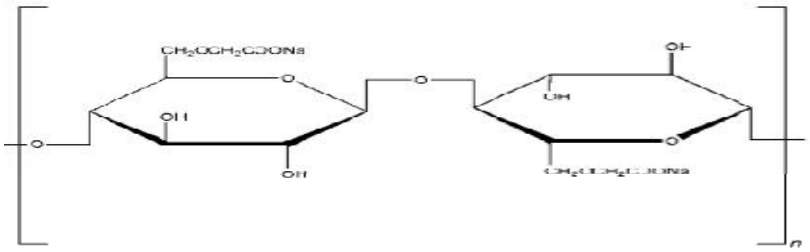
Synonyms

Akucell; Aquasorb; Blanose; cellulose gum; CMC sodium; E466; Finnfix; Nymcel; SCMC; sodium carboxy methyl cellulose; sodium cellulose glycolate; sodium CMC; Tylose CB.

Empirical Formula and Molecular Weight

The USP describes carboxymethylcellulose sodium as the sodium salt of polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Structural Formula



Description

Carboxymethylcellulose sodium occurs as a white to almost white, odourless, granular powder.

Typical Properties

Density (bulk): 0.52 g/cm3Density (tapped): 0.78 g/cm3Dissociation constant: pKa = 4.30Melting point: chars atapproximately 252^{0}C.Moisture content: typically

contains less than 10% waterSolubility: practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions.

Functional Category

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

Applications in Pharmaceutical Formulation or Technology [35]

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing properties. Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions. Higher concentrations, usually 3–6%, of the medium viscosity grade are used to produce gels that can be used as the base for applications and pastes. Uses of carboxymethylcellulose sodium.

Table No: 1 Use and Concentration of Carboxy methyl cellulose sodium

Use	Concentration (%)
Emulsifying agent	0.25–1.0
Gel-forming agent	3.0–6.0
Injections	0.05–0.75
Oral solutions	0.1–1.0
Tablet binder	1.0–6.0

POVIDONE[36]

Nonproprietary Names

BP: Povidone, JP: Povidone, PhEur: Povidonum, USP: Povidone,

Synonyms

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; poly vinyl pyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

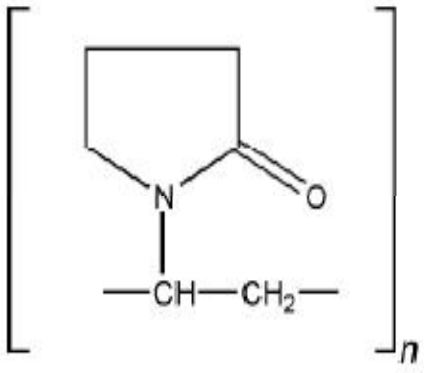
Empirical Formula and Molecular Weight

$(C_6H_9NO)n$ and 2500–3 000000

Table No: 2 Viscosity grades of Povidone

K-value	Approximate molecular weight
12	2500
15	8000
17	10 000
25	30 000
30	50000
60	400000
90	1000 000

Structural Formula



Description

Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder.

Typical Properties

Density (bulk): 0.29–0.39 g/cm^{3}Density (tapped): 0.39–0.54 g/cm^3

Melting point: softens at 150^{0}C.

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes.

Table No: 3 Use and Concentration of Povidone

Use of povidone	Use Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

ETHYL CELLULOSE[37]

Nonproprietary Names

BP: Ethyl cellulose

PhEur: Ethyl cellulosum

USPNF: Ethyl cellulose

Synonyms

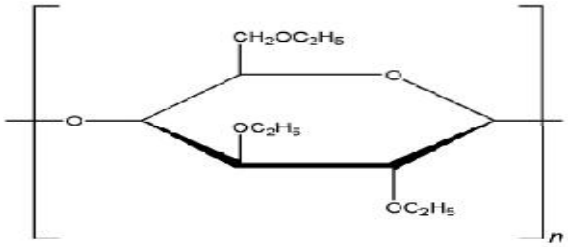
Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name

Cellulose ethyl ether

Empirical Formula $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights.

Structural Formula



Description

Ethyl cellulose is a tasteless, free-flowing, and white to light tancolored powder.

Typical Properties

Density (bulk): 0.4 g/cm^3

Solubility: ethyl cellulose is practically insoluble in glycerine,propylene glycol, and water.Specific gravity: 1.12–1.15 g/cm^3

Glass transition temperature: 129–133^{0}C

Functional Category

Coating agent; flavouring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation;

Uses of ethyl cellulose

Table No: 4 Use and Concentration of Ethyl cellulose

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

OPADRY WHITE

Opadry white aqueous moisture barrier film coating system is available in pigmented or white form only. The polymer was specially developed for the coating of oral solid dosage forms that need to be protected from environmental moisture. It is applied in an aqueous process, to form a pH independent, water soluble film coating. On a tablet this coating will function as a barrier to mask an unpleasant taste with no effect on the release profile of the drug.

Composition: HPMC, Talc, Titanium dioxide, polyvinyl alcohol

SUITABILITY OF DRUG

- Ropinirole, a nonergoline dopamine agonist, has been used to treat the motor symptoms of Parkinson's disease due to stimulation of postsynaptic dopamine D_2 type receptors.
- Ropinirole is recommended to reduce motor fluctuation in patients with advanced Parkinson's disease and usually associated with mild side effects like nausea, sleepiness, fatigue, etc when compared to other dopaminergic agonists, ergot derivatives.
- Ropinirole is USFDA approved product, 1st line of drug for the treatment of Parkinson's disease.
- Owing to its moderate elimination half-life, the immediate-release formulation is administered three-times daily. The prolonged- release formulation is associated with fewer fluctuations in plasma concentration, allowing for symptomatic treatment for the entire day with once-daily dosing.Absolute Bioavailability is 50% and Relative Bioavailability is 100% when compared to immediate release tablet forms.

Aim And Objective Of Work

AIM AND OBJECTIVE OF THE WORK

The aimof the present study was to formulate and evaluate extended release tablets of ropinirole

The main objectives of the present work are

- To reduce Dosing frequency of drug by sustaining its release.
- To Study Drug and Polymer interactions.
- To develop Stable, pharmaceutically equivalent formulation.
- Compare the developed formulation with that of reference formulation.
- To develop cost effective medicine when compared to marketed products.
- Short term stability study of the optimized formulation according to ICH Guidelines.

Plan Of Work

PLAN OF WORK

The present work was carried out to prepare Ropinirole Extended Release tablets, the stages involved in the plan of work are as follows.

- **Literature survey based on.**
  - Drug
  - Polymers
- **Characterization of innovator product**
- **Preformulation studies**
  - Preformulation studies of API
  - Compatibility studies with Excipient by HPLC
  - Finalized Selection of Excipient
- **Analytical method development**
- **Product development**
  - Selection of process
  - Formulation development
  - Process optimization
  - Finalized process
  - Finalized formula
- **Formulation Evaluation**

  Evaluation of Granules
  - Bulk and Tapped density
  - Angle of repose
  - Compressibility index

- Hausner ratio

Physico chemical Evaluation

- Thickness
- Hardness
- Friability
- Weight variation
- Drug content

❖ **Comparision of Test formulation with Reference product**

❖ **Stability Studies**

- As per ICH guidelines upto 3 months in HDPE Bottles

Materials

MATERIALS USED

Table No: 5 Materials used in formulation

S.no	Name	Manufacturers Name
1	Ropinirole HCl	Dr Reddy lab: unit(2)
2	HPMC K100M	FMC Biopolymer
3	HPMC K15M	Colorcon
4	PVP K90	Colorcon
5	Sodium Caboxy methyl cellulose	Sd fine Chemicals, Mumbai
6	Anhydrous Lactose	Qualigens Fine chemicals
7	Colloidal Sio_2	Sd fine Chemicals, Mumbai
8	Mg.stearate	Qualigens Fine chemicals
9	Ethyl cellulose	Sd fine Chemicals, Mumbai
10	Opadry white	Merck private limited
11	Tri ethyl citrate	Merck private limited
12	Isopropyl alcohol	Dr Reddy lab
13	Dichloromethane	Dr Reddy lab
14	Opadry pink	Merck private limited

EQUIPMENTS

EQUIPMENTS USED

Table No: 6 Instruments used in the formulation

S.no	Equipment	Manufacturer Name
1	Digital Balance	Sagtorious
2	Electronic Balance	Metler
3	Tapped density	Electrolaab
4	Hardness and Thickness	Varian
5	Friabilator	Roche Friabilator
6	In vitro dissolution apparatus	Electro lab
7	HPLC	Waters-Empower
8	Granulation	Roller compacter
9	Blender	Double cone blender
10	Rotary Compression Machine	Cadmach,10 Station Press
11	Coating	Gansons

Experimental Work

EXPERIMENTAL WORK

Generic drug

Generic drug is defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality an performance characteristics, and intended use.

Innovator

GlaxoSmithKline, USA

Strength

2 mg

Innovator

Tri layered formulation, Central active medicament and two placebo outer layers act as barrier layers which control surface area available for drug release.

Figure.3. Innovator Tri layered Formulation

A number of barrier compositions were formulated and tested to reach the most suitable control of the dissolution process. In particular a barrier made up of high viscosity hydroxyl propyl methylcellulose (HPMC), which is characterized by very slow hydration[38] and gelling rates, provides an excellent protection of the coated surfaces of the active core for extended times. This type of barrier, being quite impermeable to drug diffusion for long periods of time, is particularly useful to control the release of soluble drugs for once a day administration.

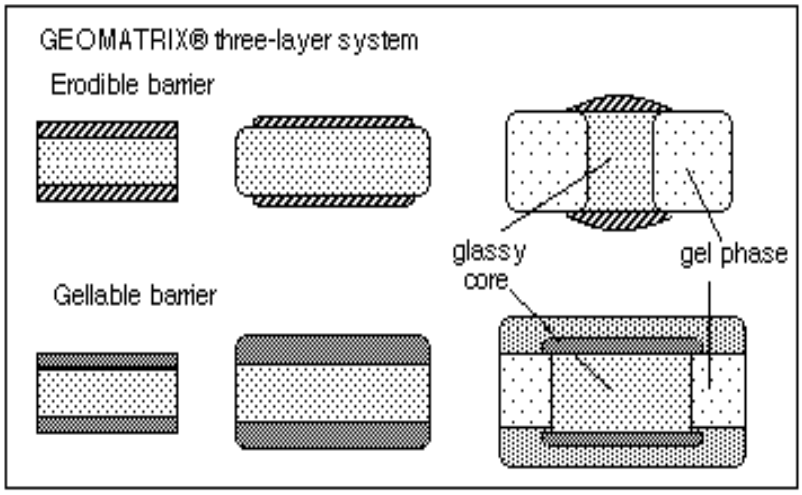


Figure.4. Geomatrix three-layer system

Characterization of Innovator product

Table No: 7 Physical characterization of Innovator

S.no	Description	Innovator (REQUIP XL)
1	Lable claim	2.28 mg of ropinirole hydrochloride equivalent to 2 mg of ropinirole
2	Shape	Biconvex, capsule-shaped
3	Hardness(kp)	12±1 kp
4	Thickness(mm)	6.6±0.2 mm
5	Weight (mg)	490 mg
6	Colour	Pink
7	Embossing	"GS & 3V2"

Inactive Ingredients: Carboxy methyl cellulose sodium, Colloidal silicon dioxide, glycerol biphenate, Hydrogenated Castor oil, Anhydrous Lactose, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Mannitol, Povidone, Ferric oxides(Black,red,yellow)

Preformulation studies[39]

Before formulation of drug substances into a dosage form, it is essential that drug polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the manufacture of a dosage form.

Particle size

Particle size distribution by Malvern instrument, it is based on laser diffraction technique. Principle involved is particle size is inversely proportional to diffraction that smaller particles diffract more and larger particles will diffract less from this percentage of particles within the microns is calculated.

Solubility

Ropinirole HCl is soluble in water and the saturation solubility was conducted in various media such as

Table No: 8 Solubility in different Media

S.no	Solubility medium	Solubility(mg/ml)
1	0.1N HCl	107.0
2	0.01N HCl	124.8
3	pH 4.5 acetate buffer	140.9
4	pH6.8 phosphate buffer	121.4
5	pH 7.2 phosphate buffer	122.7
6	Purified water	138.5

Melting point

A glass capillary tube is normally used to contain the sample for a melting point determination. Therefore the tube must have one open end into which the sample can be loaded, and one sealed end so that the capillary will retain the solid sample. Use a spatula to gather the powder into a small pile. The height of solid in the capillary should be no more than 1-2 mm. The melting point of the sample can be determined till the sample gets charred.

Table No: 9 Preformulation parameters for Active pharmaceutical ingredient

Solubility	Soluble in water and it is 133 mg/ml
Bulk density	0.27 ± 0.2 gm/ml
Tapped density	0.46±0.4 gm/ml
Compressibility index (%)	41.3%±0.5
Hausner Ratio	1.7±0.4
Melting point	248°C

Table No: 10 Flow properties For API+ Excipient mixed

1	Bulk density(g/ml)	0.4692±0.04
2	Tapped density(g/ml)	0.55±0.03
3	Carr's index	14.6±0.52
4	Hausner ratio	1.17±0.03
5	Angle of repose(Ɵ)	28.24±1.86

Drug Excipient Compatibility

Based on innovator composition and availability data following listed Excipients were selected. Drug and Excipients were passed through 40 mesh screen and mixed uniformly and loaded in glass vials as per the ratios given as follows[40]

Table No: 11 Ratios of Drug-Excipient

S.no	Excipient	Ratio (Drug –Excipient)
1	HPMC K100M	1:20
2	HPMC K15M	1:15
3	PVP K90	1:10
4	Ethyl cellulose	1:10
5	Magnesium stearate	1:5
6	Colloidal silicon dioxide	1:5
7	Stearic acid	1:5
8	Glyceryl stearate	1:5
9	PEG 6000	1:5
10	Citric acid	1:10
11	Triethylcitrate	1:2
12	Anhydrous Lactose	1:10
13	Opadry white	1:5
14	Opadry pink	1:5

Table No: 12 Impurities in Initial and Final week

Ingredient	**Initial week Impurities**					**Fourth week Impurities**				
	Desproyl	N-Methyl OH	3-OXO	N-oxide	**Total**	Despropyl	N-Methyl OH	3-OXO	N-oxide	**Total**
HPMC K100M	0.1268	ND	0.1932	ND	**0.3200**	0.1143	0.0108	0.1549	ND	**0.2800**
PVP K90	0.0956	ND	0.1398	**0.0560**	**0.2914**	0.0943	0.0125	0.0791	**0.4106**	**0.5965**
Ethyl cellulose	0.1403	ND	**0.2520**	ND	**0.3923**	0.1092	ND	**0.4674**	0.0261	**0.6027**
Mg. Stearate	0.1119	ND	0.1740	0.0066	**0.2925**	0.1133	ND	0.1918	ND	**0.3051**
Colloidal sio2	0.1253	ND	**0.4679**	0.0086	**0.6018**	0.1340	ND	**1.369**	ND	**1.5030**
Stearic Acid	0.1005	ND	0.1752	ND	**0.2757**	0.1478	ND	0.2494	ND	**0.3972**
Glyceryl stearate	0.1246	ND	**0.2309**	ND	**0.3555**	0.1142	ND	**0.4063**	0.0104	**0.5309**
PEG	0.11	ND	0.18	ND	**0.29**	0.2006	ND	0.148	0.08	**0.433**

6000	30		06		**36**			7	46	**9**
Tri ethyl citrate	0.0822	ND	0.1415	ND	**0.2237**	0.1403	ND	0.2098	ND	**0.3501**
Citric acid	0.0749	ND	0.3430	ND	**0.4179**	0.0681	ND	**14.0203**	0.0432	**14.1316**
An. Lactose	0.1367	ND	0.2097	ND	**0.3464**	0.1263	ND	0.1806	ND	**0.3069**
Opadry white	0.1296	ND	0.1895	ND	**0.3191**	0.1250	ND	0.1840	0.0258	**0.3348**
Opadry pink	0.1315	ND	0.2023	ND	**0.3338**	0.1611	ND	0.3311	ND	**0.4922**

Finalized selection of Excipients

For the development of an extended release dosage form a polymer with slow gelling property like HPMCK 100M is required. Since ropinirole is absorbed through out GIT, the matrix must also possess the capability of controlling the drug release over 24hrs for which fast gelling polymers like HPMCK 15M was used for obtaining precise control over the initial phases of release of the drug. Carboxy methyl cellulose sodium provides a synergistic effect. Povidone, a release modifier was used to obtain completeness of release from the matrix. Colloidal silicon dioxide acts as glidant to improve the flow of blend. Magnesium stearate was used as lubricant

Table No: 13 Finalized Selection of Excipients

S.no	Ingredient	Pharmaceutical function
1	HPMC K100M	Rate controlling polymer
2	HPMC K15M	Rate controlling polymer
3	Sodium carboxy methyl cellulose	Rate controlling polymer
4	PVPK 90	Rate controlling polymer
5	Anhydrous Lactose	Diluent
6	Colloidal Sio2	Anti-adherent
7	Mg.stearate	Lubricant
Functional coating		
8	Ethyl cellulose	Coating agent
9	Opadry white	Channel forming agent
10	Triethyl citrate	Plasticizer
11	Dichloromethane	Coating vehicle
12	Isopropyl alcohol	Coating vehicle
Film coating		
13	Opadry pink	Coating agent
14	Purified water	Coating vehicle

ANALYTICAL METHOD DEVELOPMENT

Innovator medium (pH 4 Citrate buffer)

Mix 5ml of 0.2M Citric acid and 85ml of 0.2M disodium citrate and dilute to 100ml with purified water. if required adjust pH to 4 with dil.NaOH

0.2M Citric acid

42.03gm of citric acid Monohydrate dissolved in 1000ml purified water

0.2M Disodium citrate dihydrate

58.82gm of disodium citrate dihydrate in 1000ml purified water

Table No: 14 Requirements in Dissolution

Medium	pH 4 Citrate buffer
Quantity	500ml
Apparatus	USP Type 2(paddle)
RPM	100 rpm
Temperature	37 ± 0.5^{0}c

DISSOLUTION BY HPLC[41]

Mobile phase: Buffer: Acetonitrile (70:30)

Standard stock solution

Weigh accurately about 73 mg of Ropinirole HCl Reference/working standard to 200ml volumetric flask add 130 ml milliQ water sonicate and made up to the mark.

Standard Preparation

Pipette 5ml of standard stock into 100ml volumetric flask and dilute through milliQ water, filter through 0.2µm whattman filter paper[42]

Equipment - Waters type with UV detector

Column Temperature - 30^0c

Flow Rate - 1.2ml/min

Injection volume - 60µL

System suitability

Calculation: Tailing not more than 2[43]

Inject 60 µL Portion of dissolution medium of test preparation

Qty of Ropinirole dissolved in n^{th} time interval

$$\frac{At}{As} \times \frac{Ws}{200} \times \frac{5}{100} \times \frac{500}{N} \times \frac{25}{5} \times \frac{P}{100} \times \frac{100}{L}$$

A_t -Peak Area of test preparation in n^{th} time

A_s –Peak Area of standard preparation

w_s- Weight of Ropinirole HCl working standard taken in mg

P -Potency of Ropinirole working standard

N –No. of tablets taken

L -Labelled amount of Ropinirole (2mg)

PRODUCT DEVELOPMENT

Product development involves two stages; it involves Formulation and Process development.

Selection of process [44]

Direct compression

Milling the drug and excipients like HPMC, CMC sodium, anhydrous lactose, povidone through 40 mesh screen and mixing of drugs and excipients then go for direct compression of tablet

Wet granulation

Millingand mixing of drugs and excipients like HPMC,CMC sodium, Anhydrous lactose, prepare the povidone binder solution and is introduced in RMG granulator which contained blending material and granules is formed by impeller and chopper amperage adjustment and wet granules is formed. The formed granules are dried in fluidised bed dryer. The dried granule is placed in blender and colloidal silicon dioxide and magnesium stearate is added, then compress the tablet.

Dry granulation

Sift the material through 30 mesh and mixing of drug and excipients like HPMC, Sodium CMC, Anhydrous lactose, pass through roller compactor results in formation of ribbon shaped flakes then pass the flakes in vibratory granulator formation of granules. These granules passed through blender where colloidal silicon dioxide and magnesium stearate is added and compress the tablet.

From above issues we consider that dry granulation is preferred method and all the optimization of formula is done with dry granulation process

Figure.5. Roller compactor

Formulation development

Formulation development involves following stages of optimization of excipients.

Optimization of rate controlling polymers

During this stage, optimization of polymers using Hydrophilic[45] and Hydrophobic polymers was done. The percentage of drug release using Hydrophilic polymers is more compared to hydrophobic polymers and therefore finalised use of Hydrophilic polymers. In all these dissolution performed with H.P.L.C, and the average of 4 tablets is mentioned here.

Procedure

- Rinse API with Anhydrous Lactose part 1 and pass through 30 mesh screen, Sift together HPMC K100M, HPMC K15M[46] Castor oil, Stearic acid in four different formulation and pass through 30 mesh screens.
- Sift the contents of Anhydrous Lactose part 2 with colloidal silicon dioxide and magnesium stearate of part 1 and pass through 30 mesh screen and to this PVP K90 is added.
- Blend the entire contents for 10 minutes and subject the material to roller compaction. The soft compacts were milled through 5mm screen with knives forward.
- Granules were sifted through 24 mesh, Blend the granules using colloidal silicon dioxide and Magnesium stearate of part 2.
- Compression of Lubricated blend using 12.5×7.0 mm punches in 10 station rotary compression machine.

Table No: 15 Optimization of Rate controlling polymers

Ingredients	Formulation code			
	F1(mg)	**F2(mg)**	**F3(mg)**	**F4(mg)**
Ropinirole HCl	2.28	2.28	2.28	2.28
HPMC K100M	240	185	-	-
HPMC K15M	60	55	-	-
PVP K90	10	10	10	10
Castor oil	-	-	200	184
Stearic acid	-	-	56	54
Anhydrous Lactose	83.22	143.22	127.22	145.22
Colloidal Sio_2	3	3	3	3
Mg.stearate	1.5	1.5	1.5	1.5

Percentage of drug release

The tablets prepared by four formulationsare taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample.

Table No: 16 Percentage drug release during optimization of polymers

Time(h)	% Drug release (Avg of 4 Tablets)			
	F1	F2	F3	F4
0	0	0	0	0
1	17±1.0	14±0.3	10±1.0	09±0.3
2	24±0.8	22±0.5	17±1.2	15±0.5
4	39±0.1	33±0.2	21±1.0	22±0.9
8	57±0.0	49±0.9	32±1.1	34±1.0
12	70±0.4	62±0.8	44±1.0	42±1.1
16	79±1.0	72±1.0	49±1.2	50±0.2
20	84±0.9	76±1.2	52±1.0	57±1.0
24	87±0.5	80±1.3	65±1.2	63±1.0

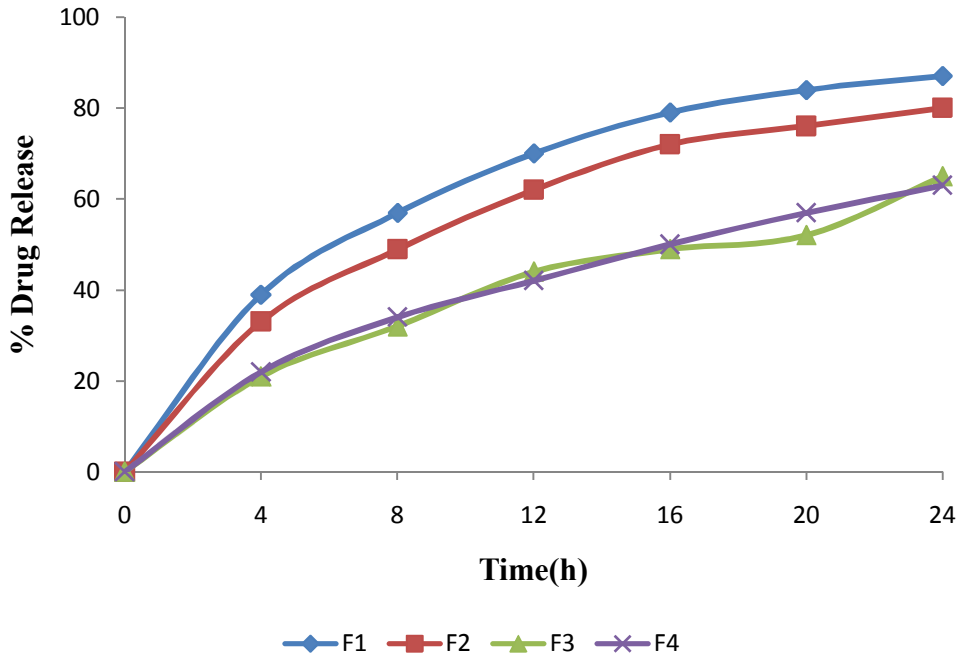


Figure.6. Time v/s % Drug release (optimization of polymers)

Optimization of PVP K90

Release of the entrapped drug from a highly viscous and strong matrix is not easy. Once the matrix imbibes sufficient water, it increases in path length and blocks channeling due to which release tends to stop leading to an incomplete release. A release modifier which sufficiently modulates the rigidity of matrix and is necessary for obtaining completeness of release

Procedure

- Rinse API with Anhydrous Lactose part 1 and pass through 30 mesh screen, Sift together HPMC K100M and HPMC K15M and pass through 30 mesh screen.
- Sift the contents of Anhydrous Lactose part 2 with colloidal silicon dioxide and magnesium stearate of part 1 and pass through 30 mesh screen and to this PVP K90 is added.
- Blend the entire contents for 10 minutes and subject the material to roller compaction. The soft compacts were milled through 5mm screen with knives forward.
- Granules were sifted through 24 mesh, Blend the granules using colloidal silicon dioxide and Magnesium stearate of part 2.
- Compression of Lubricated blend using 12.5×7.0 mm punches in 10 station rotary compression machine.

Table No: 17 Optimization of PVP K90

Ingredients	Formulation code			
	F1(1) (mg)	F1(2) (mg)	F1(3) (mg)	F1(4) (mg)
Ropinirole HCl	2.28	2.28	2.28	2.28
HPMC K100M	240	240	240	240
HPMC K15M	60	60	60	60
PVP K90	50	55	40	60
Anhydrous Lactose	43.22	38.22	53.22	33.22
Colloidal Sio_2	3	3	3	3
Mg.stearate	1.5	1.5	1.5	1.5

Percentage of drug release

The tablets prepared by four formulations are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample

Table No: 18 Percentage drug release during optimization of PVP K90

Time(h)	% Drug release (Avg of 4 Tablets)			
	F1(1)	F1(2)	F1(3)	F1(4)
0	0	0	0	0
1	16±1.2	18±0.4	14±0.4	20±1.2
2	27±1.0	28±1.2	23±1.0	30±0.1
4	42±1.0	44±1.2	38±0.9	48±0.4
8	63±1.2	66±1.0	62±1.2	68±0.5
12	74±1.1	78±0.5	70±0.3	80±0.2
16	82±1.2	86±1.2	78±0.9	89±0.9
20	88±0.9	90±0.9	84±0.8	93±0.7
24	92±0.1	96±1.0	90±0.7	98±0.9

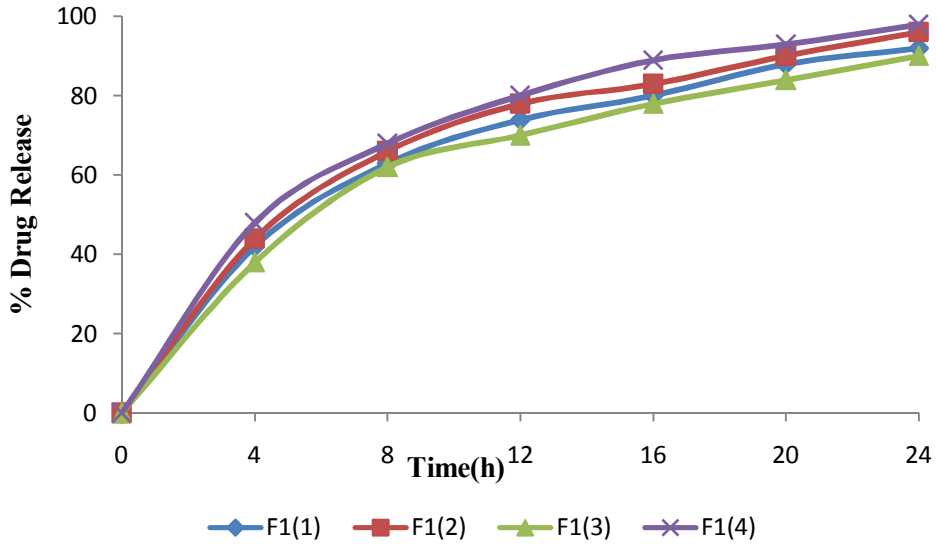


Figure.7. Time v/s % Drug release (Optimization of PVPK 90)

Optimization of Sodium carboxy methylcellulose

Carboxy methyl cellulose sodium was incorporated to exhibit synergistic effect along with Hypromellose in controlling the release throughout the matrix. For modulating matrix strength and rigidity, it was necessary to add a fast gelling agent like Sodium carboxy methyl cellulose**.**

Procedure

- Rinse API with Anhydrous Lactose part 1 and pass through 30 mesh screen, Sift together HPMC K100M and HPMC K15M and pass through 30 mesh screen.
- Sift the contents of Anhydrous Lactose part 2 with colloidal silicon dioxide and magnesium stearate of part 1 and pass through 30 mesh screen and to this PVP K90 and Sodium carboxy methyl cellulose is added.
- Blend the entire contents for 10 minutes and subject the material to roller compaction. The soft compacts were milled through 5mm screen with knives forward. Granules were sifted through 24 mesh, Blend the granules using colloidal silicon dioxide and Magnesium stearate of part 2.
- Compression of Lubricated blend using 12.5×7.0 mm punches in 10 station rotary compression machine.

Table No: 19 Optimization of Sodium carboxy methyl cellulose

Ingredients	Formulation code		
	F1(4)(1) (mg)	F1(4)(2) (mg)	F1(4)(3) (mg)
Ropinirole HCl	2.28	2.28	2.28
HPMC K100M	240	240	240
HPMC K15M	60	60	60
PVP K90	-	35	60
Sodium carboxy methyl cellulose	75	40	15
Anhydrous Lactose	18.72	18.72	18.72
Colloidal Sio_2	2	2	2
Mg.stearate	2	2	2

Percentage of drug release

The tablets prepared by four formulations are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample

Table No: 20 Percentage drug release during optimization of Sodium carboxy methyl cellulose

Time(h)	% Drug release (Avg of 4 Tablets)		
	F1(4)(1)	F1(4)(2)	F1(4)(3)
0	0	0	0
1	12±0.7	14±0.8	18±0.4
2	20±0.9	23±1.2	28±0.7
4	32±1.2	34±1.0	40±1.0
8	50±0.5	53±0.5	62±0.2
12	63±0.5	67±0.5	74±0.4
16	73±0.2	77±0.7	82±0.3
20	80±0.9	86±0.4	90±0.5
24	87±1.0	92±1.0	98±0.7

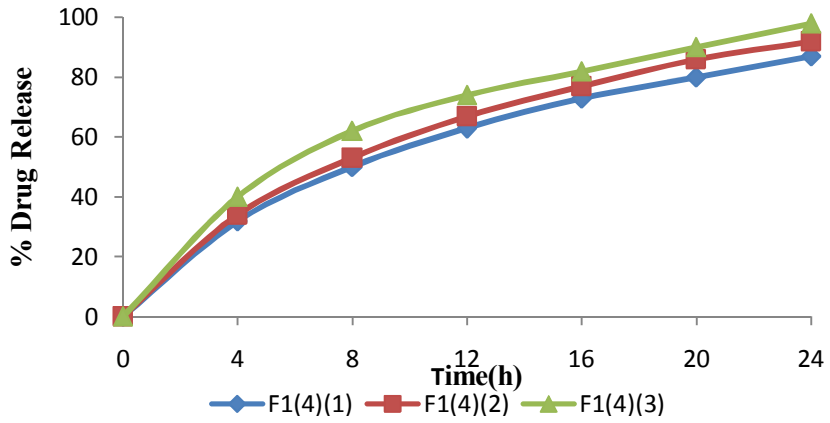


Figure.8. Time v/s % Drug release(Optimization of Sodium carboxy methyl cellulose)

Optimization of functional coating formula

Since the drug is moisture sensitive, to protect the drug from atmosphere Hydrophobic polymer is used and to have drug release Opadry white is used which acts as channel forming agent and thereby drug release is seen.

Procedure

- Rinse API with Anhydrous Lactose part 1 and pass through 30 mesh screen, Sift together HPMC K100M and HPMC K15M and pass through 30 mesh screen.
- Sift the contents of Anhydrous Lactose part 2 with colloidal silicon dioxide and magnesium stearate of part 1 and pass through 30 mesh screen and to this PVP K90 and Sodium carboxy methyl cellulose is added.
- Blend the entire contents for 10 minutes and subject the material to roller compaction. The soft compacts were milled through 5mm screen with knives forward.
- Granules were sifted through 24 mesh, Blend the granules using colloidal silicon dioxide and Magnesium stearate of part 2.
- Compression of Lubricated blend using 12.5×7.0 mm punches in 10 station rotary compression machine. Functional coating is needed since the drug is moisture sensitive, to protect the exposure to atmosphere Hydrophobic polymer like Ethyl cellulose and Opadry white is used which acts as channel forming agent and thereby drug release is seen, and three optimization is done

Table No: 21 Optimization of Functional Coating

Ingredients	Formulation code		
	F1(4)(3)(1) mg	F1(4)(3)(2) mg	F1(4)(3)(3) mg
Ropinirole HCl	2.28	2.28	2.28
HPMC K100M	240	240	240
HPMC K15M	60	60	60
PVP K90	60	60	60
Sodium carboxy methyl cellulose	15	15	15
Anhydrous Lactose	18.72	18.72	18.72
Colloidal Sio_2	2	2	2
Mg.stearate	2	2	2
Total	400	400	400
Ethyl cellulose	10.78	8.62	4.31
Opadry white	10.78	12.93	17.25
Tri ethyl citrate	0.44	0.44	0.44
Isopropyl alcohol	q.s	q.s	q.s
Dichloromethane	q.s	q.s	q.s

Percentage of drug release

The tablets prepared by three formulations are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample.

Table No: 22 Percentage drug release during optimization of Functional Coating

Time(h)	% Drug release (Avg of 4 Tablets)		
	F1(4)(3)(1)	F1(4)(3)(2)	F1(4)(3)(3)
0	0	0	0
1	0	06±0.4	16±0.6
2	2±0.6	18±1.3	28±0.6
4	10±0.2	35±0.6	44±0.6
8	32±0.2	57±1.2	65±0.2
12	51±1.0	69±0.5	78±0.6
16	66±1.0	78±0.3	88±0.6
20	77±1.2	87±1.2	95±0.0
24	85±0.5	92±0.8	98±0.2

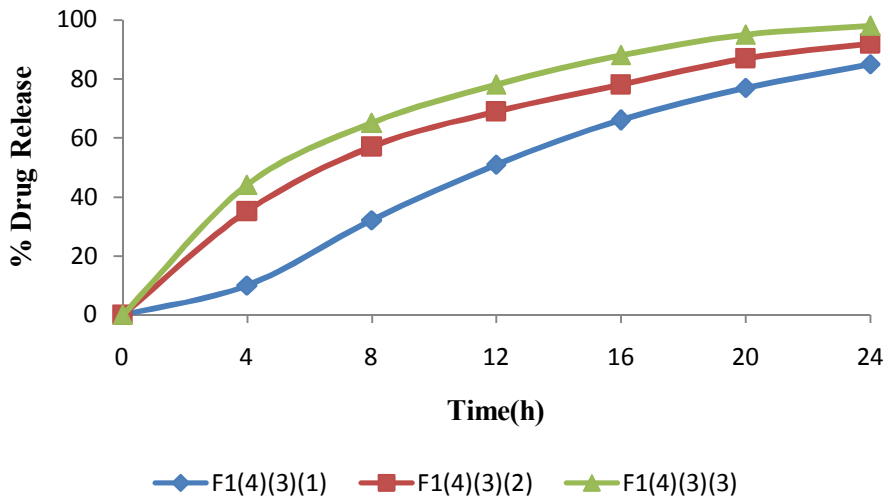


Figure.9. Time v/s % Drug release(Optimization of functional coating formula)

Process optimization

During process Optimization the finalized formula is taken and tablets are prepared by three process, like direct compression, dry granulation and wet granulation. The percentage of drug release is almost same in all three process but there are issues in wet granulation and direct compression hence finalized the process of dry granulation

Table No: 23 Optimization of process

Ingredients	Direct compression	Dry granulation	Wet granulation
Ropinirole HCl	2.28	2.28	2.28
HPMC K100M	240	240	240
HPMC K15M	60	60	60
PVP K90	60	60	60
Sodium carboxy methyl celluolse	15	15	15
Anhydrous Lactose	18.72	18.72	18.72
Colloidal Sio_2	2	2	2
Mg.stearate	2	2	2
Purified water	-	-	q.s

Percentage of drug release

The tablets prepared by three formulations are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample.

Table No: 24 Percentage drug release during Optimization of Process

Time(h)	% Drug release (Avg of 4 Tablets)		
	Direct compression	Dry granulation	Wet granulation
0	0	0	0
1	13±0.2	15±0.4	14±0.5
2	22±0.6	25±0.4	20±0.7
4	36±0.7	59±0.7	35±0.2
8	58±0.2	65±0.9	56±0.4
12	74±0.4	78±0.2	72±0.6
16	82±0.6	84±0.4	80±0.6
20	89±0.8	91±0.5	86±0.8
24	94±0.4	96±0.7	92±0.5

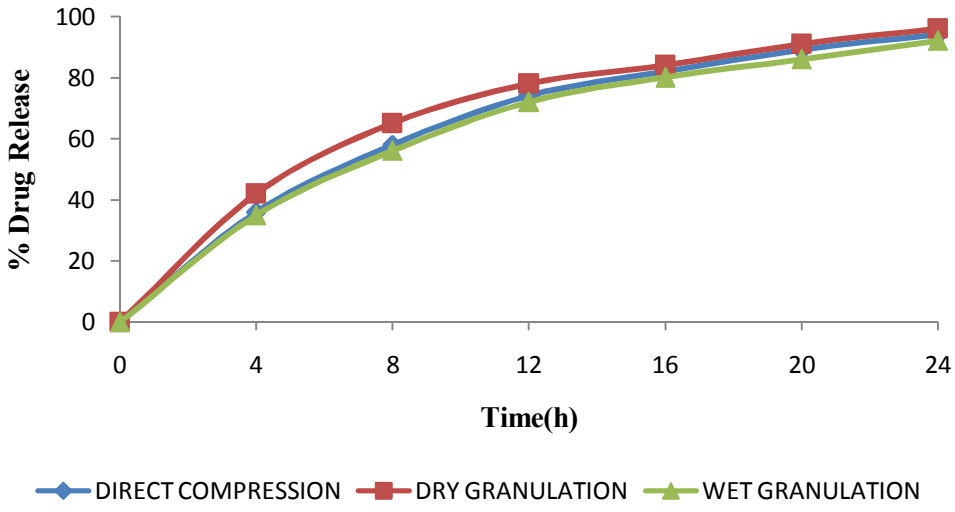


Figure No.10. Time v/s % Drug release(Optimization of Process)

Table No: 25 Final Optimized Formula

Ingredient	2mg (Qty in mg)
Ropinirole HCl	2.28
HPMC K100M	240
HPMC K15M	60
PVP K90	60
Sodium carboxy methyl cellulose	15
Anhydrous Lactose	18.72
Colloidal Sio_2	2
Mg.stearate	2
Total	400
Functional coating	
Ethyl cellulose	4.31
Opadry white	17.25
Tri ethyl citrate	0.44
Isopropyl alcohol	q.s
Dichloromethane	q.s
% Coating gain	5%
Film coating	
Opadry pink	14.77
Purified water	q.s
% Coating gain	3%
TOTAL	436.77

Formulation evaluation

Evaluation of Granules

Bulk Density (Db) [47]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by Pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the

bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = \frac{M}{Vb}$$

Where, M is the mass of powder,

Vb is the bulk volume of the powder.

Tapped Density (Dt)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2% [48]. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = \frac{M}{Vt}$$

Where, M is the mass of powder,

Vt is the tapped volume of the powder.

Angle of Repose (Ɵ) [49]

The friction forces in a loose powder can be measured by the angle of repose (**Ɵ**). It is an Indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\mathrm{Tan}(\theta) = \frac{\square}{r}$$

Ɵ= $\tan^{-1}$ (h / r)

Where,Θ is the angle of repose.h is the height in cms, r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Table No: 26 Angle of Repose as an Indication of Powder Flow Properties

Angle of repose	Flow ability
<25	Excellent
26-30	Good
31-35	Passable
>35	Very Poor

Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is give

$$Compressibility\ Index = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \text{ x } 100$$

Where, D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

Table No: 27 Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair Passable
23-35	Poor
33-38	Very Poor
<40	Very very Poor

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following Formula.

$$Hausner\ Ratio = \frac{Tapped\ density}{Bulk\ density}$$

Where, D_t is the tapped density.

D_b is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Table No: 28 Derived and flow properties of Granules of formulation

Formulation Code	Bulk Density ± SD	Tapped density ± SD	Angle of Repose ± SD	Carr's Index ± SD	Hausner's ratio ± SD
F1	0.421±0.03	0.482± 0.2	25.20 ± 0.7	12.6 ± 2.2	1.14 ± 0.2
F2	0.469 ± 1.2	0.544 ± 1.1	25.12 ± 1.2	13.8 ± 1.1	1.16 ± 1.3
F3	0.469 ± 1.8	0.550 ± 1.7	26.56 ± 1.9	14.7 ± 1.9	1.17 ±1.1
F4	0.434 ± 1.5	0.508 ± 1.6	25.20 ± 1.8	14.5 ± 1.8	1.17 ± 1.7
F1(1)	0.459 ± 1.3	0.534 ± 1.3	24.77 ± 1.3	14.0 ± 1.4	1.16 ± 1.2
F1(2)	0.493 ± 0.9	0.570 ± 1.0	26.34 ± 1.4	13.5 ± 1.1	1.16 ± 1.2
F1(3)	0.471±0.02	0.542± 0.2	27.60 ± 0.4	13.1± 2.1	1.15 ± 0.3
F1(4)	0.521 ± 0.8	0.601 ± 0.9	24.32 ± 1.5	13.3 ± 0.8	1.15 ± 0.6
F1(4)(1)	0.458 ± 0.4	0.522 ± 0.5	22.78 ±1.2	12.2 ± 0.3	1.14 ± 0.2
F1(4)(2)	0.462 ± 0.5	0.528 ± 0.6	23.12 ± 1.4	12.5 ± 0.7	1.14 ± 0.8
F1(4)(3)	0.516 ± 0.7	0.582 ± 0.8	23.56 ± 1.6	11.3 ± 0.6	1.12 ± 0.5

Physico-chemical evaluation of tablets

Thickness and hardness

The Thickness and Hardness of the each tablet was measured by using Varian automatic Thickness and Hardness tester and the average Thickness and Hardness in mm and kp was calculated.

Friability[50]

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Weight variation[51]

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} X 100$$

Table No: 29 Avg wt of Tablet and %Deviation

Avg.wt of Tablet	% Deviation
130mg or less	±10
More than 130mg but less than 324mg	±7.5
More than 324mg	±5

Assay (Drug content) [52]

Mobile phase: Buffer: Acetonitrile (80:20)

Diluents: Dil-1 (Acetonitrile: Methanol-80:20)

Dil-2 (milliQ water)

Standard stock preparation

Transfer accurately weighed amount of 55mg reference standard to 200 ml volumetric flask add 80ml of diluents-2,sonicate to dissolve the material and dilute the volume with diluents-2 and mix well.

Standard preparation

Pipette 5ml of std.stock solution to 100ml volumetric flask and dilute the volume with diluent-2.

Test preparation

Transfer 10 tablets into 500ml volumetric flask, add about 200ml methanol and150ml dil-1sonicate for 40 min with intermediate shaking. Centrifuge the above solution for 10 min. pipette out 5ml of clear supernatant into 25ml volumetric flask and made upto mark with diluent-2.

Equipment -Waters type with UV detector

Column Temperature -30^0c

Flow Rate -1.2ml/min

Injection volume -80µL

Qty of Ropinirole present in portion of tablet is

$$\frac{A_t}{A_s} \times \frac{W_s}{200} \times \frac{5}{100} \times \frac{500}{P} \times \frac{25}{5} \times \frac{N}{100} \times \frac{100}{L}$$

A_t -Peak Area of test preparation in n^{th} time

A_s –Peak Area of standard preparation

w_s- Weight of Ropinirole HCl working standard taken in mg

P -Potency of Ropinirole working standard

N –No. of tablets taken

L -Labelled amt of Ropinirole (2mg)

Table No: 30 Evaluation of Tablets of Formulation

Formulation Code	Hardness (kp)	Thickness (mm)	Friability	% Weight variation	Assay (%)
F1	08 ± 0.7	5.4 ± 0.6	0.30 ± 0.8	1.2 ± 0.6	92 ± 0.5
F2	10 ± 0.2	5.3 ± 1.7	0.36 ± 0.5	2.4 ± 0.4	90 ± 0.6
F3	14 ± 0.6	5.5 ± 1.5	0.40 ± 0.4	2.8 ± 0.3	86 ± 0.5
F4	16 ± 0.7	5.4 ± 0.3	0.25 ± 0.2	3.2 ± 0.4	88 ± 1.3
F1(1)	10 ± 0.3	5.5 ± 0.2	0.35 ± 0.5	2.8 ± 0.2	92 ± 1.2
F1(2)	12 ± 0.2	5.6 ± 0.4	0.55 ± 0.6	2.6 ± 0.3	94 ± 0.7
F1(3)	10 ± 1.4	5.8 ± 0.1	0.45 ± 0.2	2.2 ± 0.4	96 ± 1.2
F1(4)	12 ± 0.8	5.7 ± 0.2	0.40 ± 0.3	2.4 ± 0.4	94 ± 0.2
F1(4)(1)	14 ± 1.0	5.9 ± 0.3	0.30 ± 0.4	1.9 ± 0.6	96 ± 0.5
F1(4)(2)	13 ± 0.8	5.6 ± 0.4	0.28 ± 0.6	1.8 ± 0.2	95 ± 0.3
F1(4)(3)	10 ± 0.5	5.5 ± 0.8	0.20 ± 0.4	1.6 ± 0.5	99 ± 0.2

IN-VITRO DRUG RELEASE STUDY[53]

The USP type IIrotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 500 ml of Citrate buffer pH 4. The release study was performed at 37 ± 0.5^0 C, with a rotation speed of 100 rpm. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, and were analyzed in H.P.L.C.

The kinetic models used were a zero-order equation, higuchi's model and peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. i.e. Cumulative percentage release of drug Vs Square root of time (Higuchi's)[54]and Log cumulative percentage release Vs Log time (Peppas)[55]. To know the mechanism of drug release of Ropinirole from the tablet the drug release data was fit into higuchi's models.

Table No: 31 In-vitro Drug release and Higuchi data for formulations F1- F1 (4)

Time (h)	Sqrt of time	% Cumulative drug release							
		F1	F2	F3	F4	F1(1)	F1(2)	F1(3)	F1(4)
0	0	0	0	0	0	0	0	0	0
1	1.000	17	14	10	09	16	18	14	20
2	1.414	24	22	17	15	27	28	23	30
4	2.000	39	33	21	22	42	44	38	48
8	2.828	57	49	32	34	63	66	62	68
12	3.464	70	62	44	42	74	78	70	80
16	4.000	79	72	49	50	82	86	78	89
20	4.472	84	76	52	57	88	90	84	93
24	4.898	87	80	65	63	92	96	90	98

Table No: 32Peppa's data for Formulation F1-F1 (4)

Time (h)	Log time	Log % Cumulative drug release							
		F1	F2	F3	F4	F1(1)	F1(2)	F1(3)	F1(4)
1	0	1.23	1.15	1.00	0.95	1.20	1.25	1.14	1.30
2	0.301	1.38	1.34	1.23	1.18	1.43	1.45	1.36	1.48
4	0.602	1.59	1.52	1.32	1.34	1.62	1.64	1.58	1.68
8	0.903	1.76	1.69	1.50	1.53	1.81	1.81	1.79	1.83
12	1.079	1.85	1.79	1.64	1.62	1.87	1.89	1.85	1.92
16	1.204	1.90	1.86	1.69	1.70	1.91	1.93	1.89	1.95
20	1.301	1.92	1.88	1.72	1.76	1.94	1.95	1.92	1.97
24	1.380	1.94	1.92	1.81	1.80	1.96	1.98	1.95	1.99

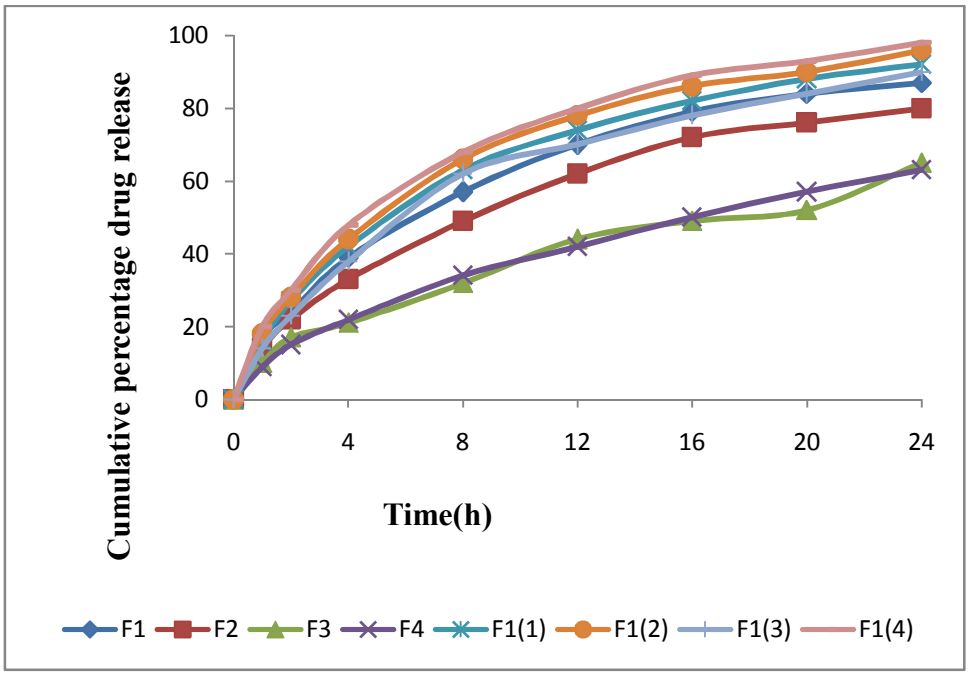


Figure No.11. *In-vitro* drug release data for formulation F1-F1 (4)

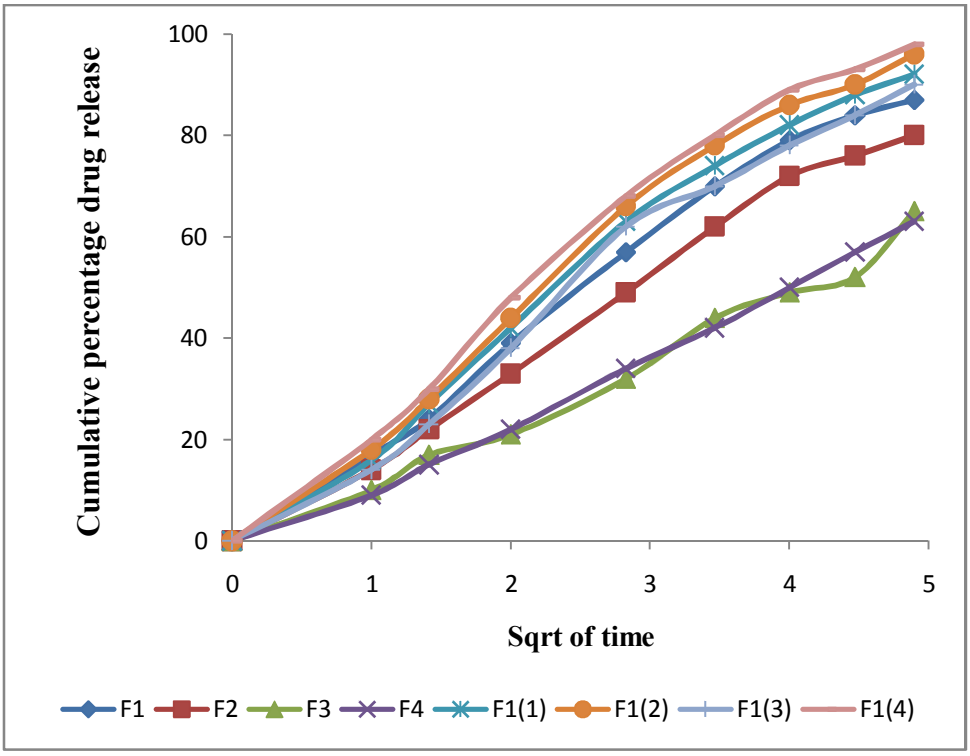


Figure No.12.Higuchi plot of formulation F1-F1 (4)

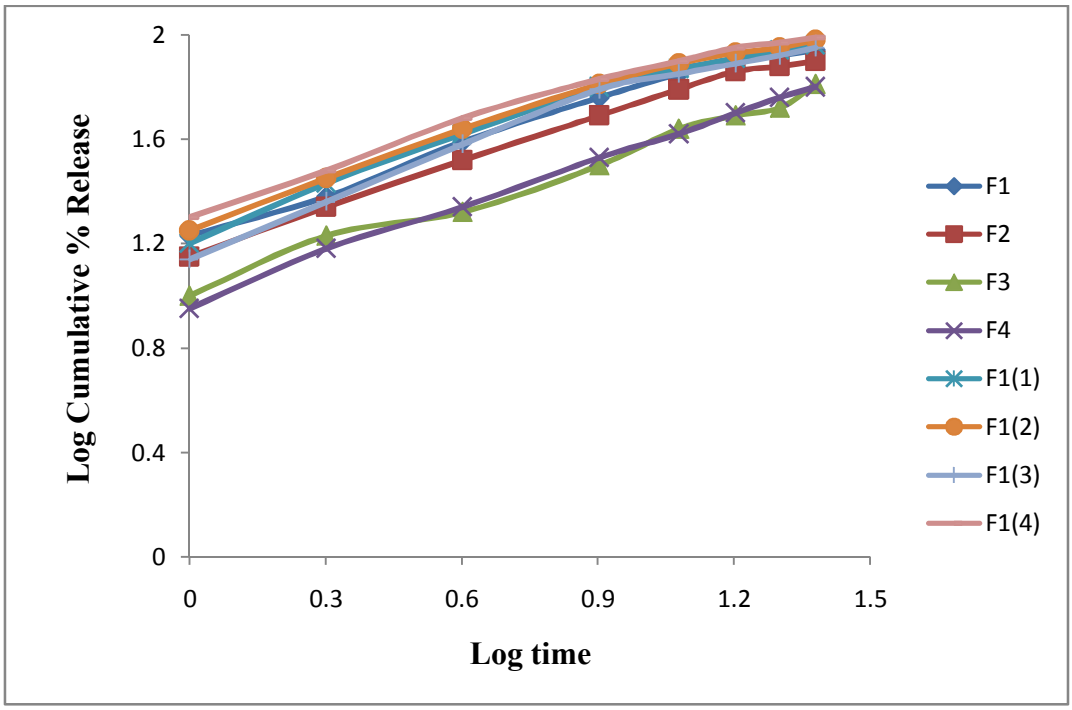


Figure No.13.Peppa's plot of formulation F1-F1 (4)

Table No: 33 In-vitro Drug release and Higuchi data for formulations F1(4)(1)- F1(4)(3(3)

Time (h)	Sqrt of time	% Cumulative drug release					
		F1(4)(1)	F1(4)(2)	F1(4)(3)	F1(4)(3)(1)	F1(4)(3)(2)	F1(4)(3)(3)
0	0	0	0	0	0	0	0
1	1.000	12	14	18	0	06	16
2	1.414	20	23	28	2	18	28
4	2.000	32	34	40	10	35	44
8	2.828	50	53	62	32	57	65
12	3.464	63	67	74	51	69	78
16	4.000	73	77	82	66	78	88
20	4.472	80	86	90	77	87	95
24	4.898	87	92	98	85	92	98

Table No: 34 Peppa's data for Formulation F1(4)(1)- F1(4)(3(3)

Time (h)	Log time	Log % Cumulative drug release					
		F1(4)(1)	F1(4)(2)	F1(4)(3)	F1(4)(3)(1)	F1(4)(3)(2)	F1(4)(3)(3)
1	0	1.07	1.15	1.25	0.84	0.78	1.21
2	0.301	1.30	1.36	1.45	1.23	1.26	1.45
4	0.602	1.51	1.53	1.62	1.42	1.54	1.64
8	0.903	1.72	1.72	1.79	1.61	1.76	1.81
12	1.079	1.80	1.82	1.87	1.72	1.84	1.89
16	1.204	1.86	1.89	1.91	1.82	1.89	1.94
20	1.301	1.91	1.93	1.95	1.89	1.94	1.98
24	1.380	1.94	1.93	1.99	1.93	1.96	1.99

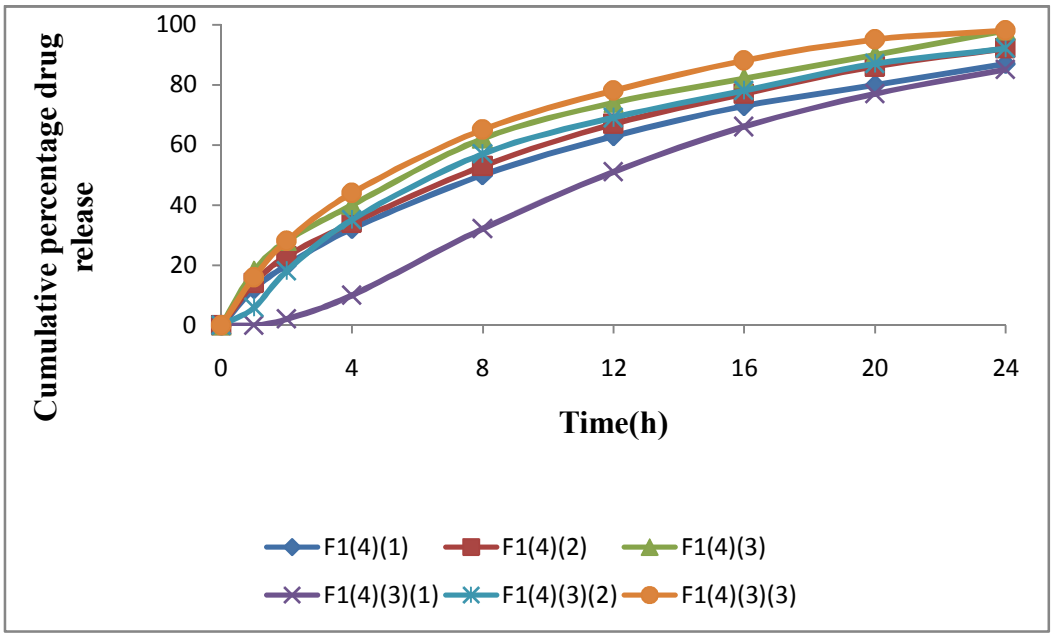


Figure No.14.*In-vitro* drug release data for formulation F1(4)(1)-F1(4)(3)(3)

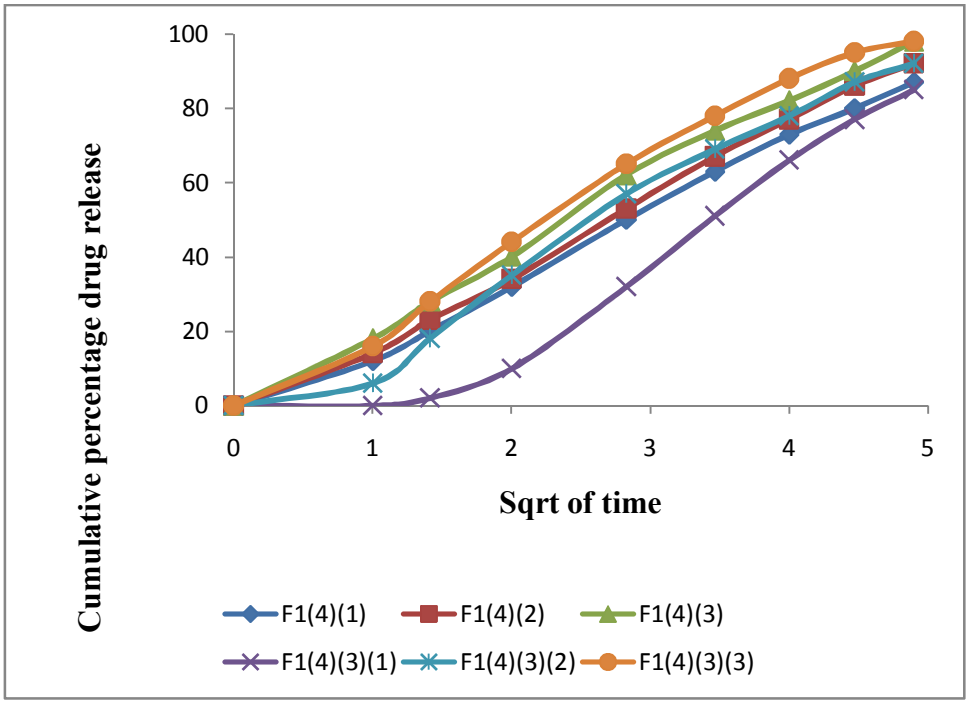


Figure No.15. Higuchi plot of formulation F1(4)(1)-F1(4)(3)(3)

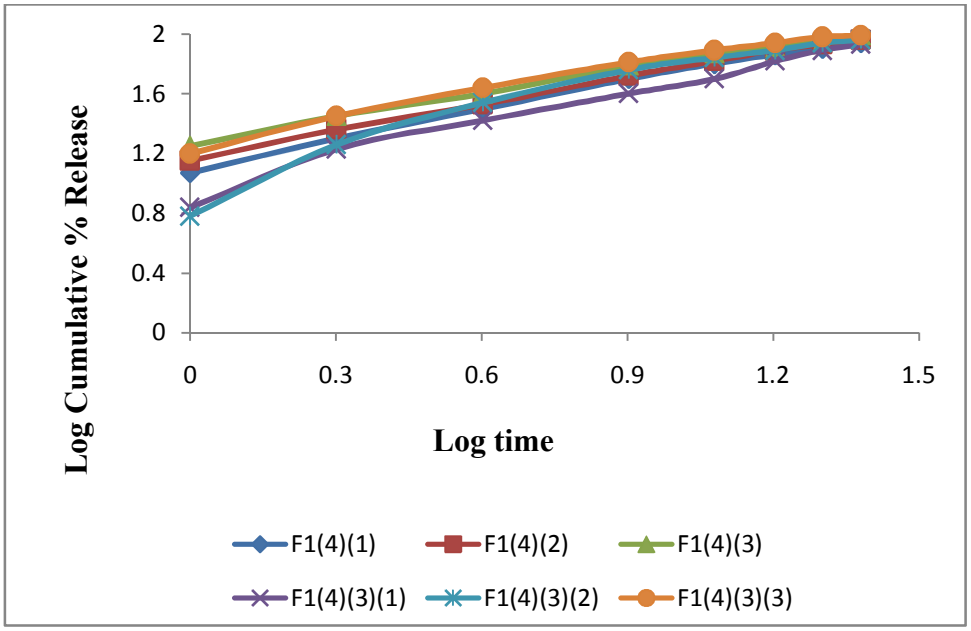


Figure No.16. Peppa's plot of formulation F1(4)(1)-F1(4)(3)(3)

IN-VITRO DRUG RELEASE STUDY WHEN COMPARED WITH INNOVATOR PRODUCT

The Tablet from the finalized or optimized formula is taken and it is compared with Innovator medium (pH 4 Citrate buffer) is used and compare the dissolution profiles of our formulation and innovator formulation[56]

Table No: 35 Requirements in Dissolution

Medium	pH 4 Citrate buffer
Quantity	500ml
Apparatus	USP Type 2(paddle)
RPM	100 rpm
Temperature	37 ± 0.5^{0}c

Table No: 36 Significance of Similarity factor

S.no	Similarity factor (f_2)	Significance
1	< 50	Test and Reference are dissimilar
2	50-100	Test and Reference are Similar
3	100	Test and Reference are Identical
4	>100	Equation yield negative value

Percentage of drug release

The tablets prepared by Finalized formulation are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample

Table No: 37 Percentage drug release of Finalized and Innovator Formulation

Time(h)	% Drug release (Avg of 10 Tablets)	
	Finalized formulation	Innovator formulation
0	0	0
1	11±0.1	14±0.4
2	18±0.2	22±0.3
4	29±0.2	36±0.2
8	48±0.3	55±0.5
12	65±0.4	70±0.2
16	79±0.3	82±0.7
20	89±0.2	90±0.6
24	95±0.5	96±0.2

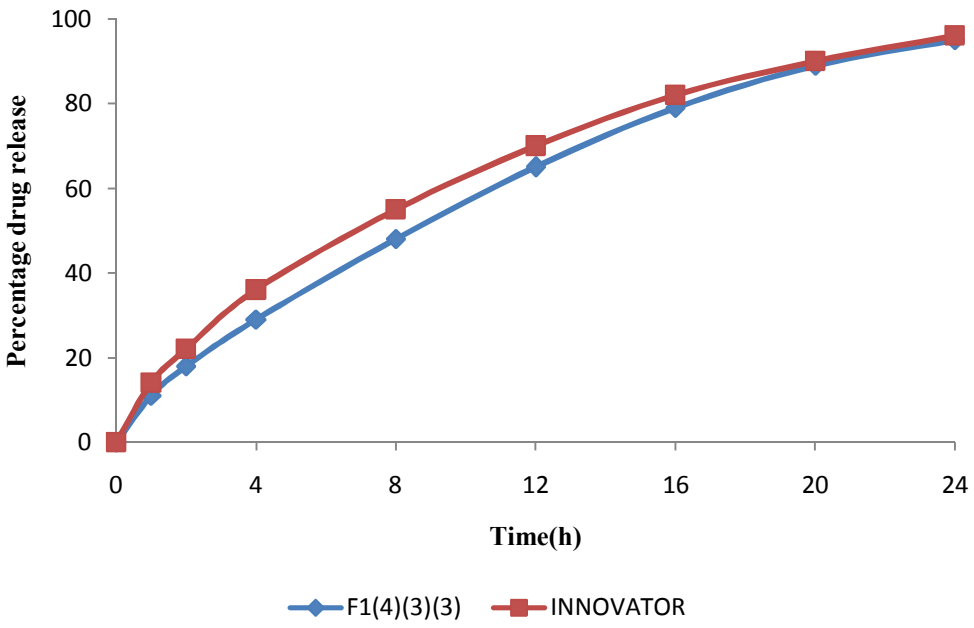


Figure.17.Comparitive dissolution profile in pH 4 Citrate buffer

Comparitive dissolution profile in pH 6.8 Phosphate buffer

The Tablet from the finalized or optimized formula is taken and it is compared with Innovator medium (pH 6.8 Phosphate buffer) is used and compare the dissolution profiles of our formulation and innovator formulation

Table No: 38 Requirements in Dissolution Medium of pH 6.8 Phosphate buffer

Medium	pH 6.8 Phosphate buffer
Quantity	500ml
Apparatus	USP Type 2(paddle)
RPM	100 rpm
Temperature	37 ± 0.5^{0}c

Percentage of drug release

The tablets prepared by the Finalized formulation are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample.

Table No: 39 Percentage drug release of Finalized v/s Innovator Formulation in pH 6.8 Phosphate buffer

Time(h)	% Drug release (Avg of 10 Tablets)	
	Finalized formulation	**Innovator formulation**
0	0	0
1	12±0.2	08±0.5
2	21±0.1	14±0.2
4	35±0.3	28±0.5
8	54±0.4	46±0.4
12	66±0.5	62±0.1
16	75±0.3	74±0.4
20	82±0.2	85±0.3
24	89±0.3	96±0.1

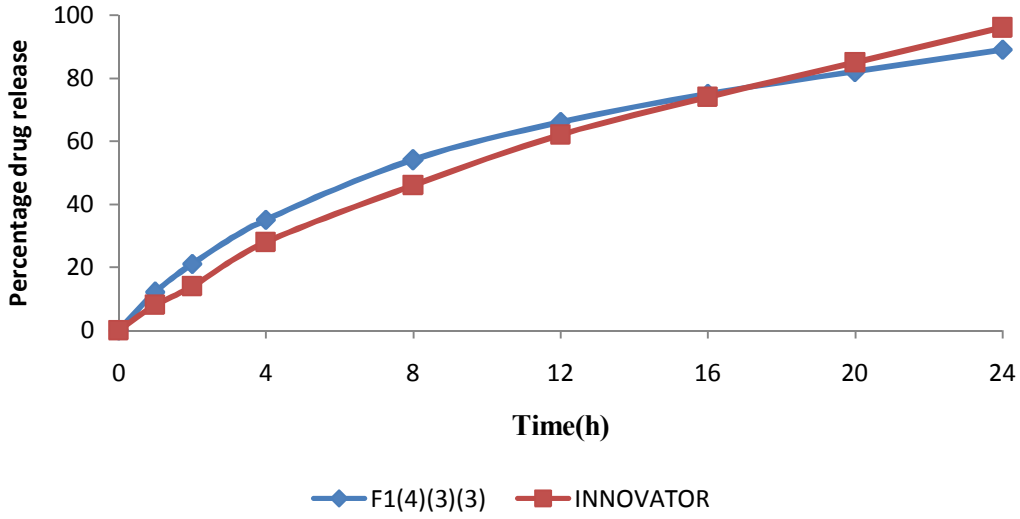


Figure.18. Comparitive dissolution profilein pH 6.8 Phosphate buffer

Comparitive dissolution profile in pH 1.2 HCl

The Tablet from the finalized or optimized formula is taken and it is compared with Innovator medium (pH 1.2 HCl) is used and compare the dissolution profiles of our formulation and innovator formulation

Table No: 40 Requirements in Dissolution Medium of pH 1.2 HCl

Medium	pH 1.2 HCl
Quantity	500ml
Apparatus	USP Type 2(paddle)
RPM	100 rpm
Temperature	37 ± 0.5^{0}c

Percentage of drug release

The tablets prepared by the Finalized formulation are taken and perform the dissolution in USP type 2 apparatus and samples are withdrawn at suitable intervals and percentage is calculated in HPLC by calculating peak areas of test sample.

Table No: 41 Percentage drug release of Finalized v/s Innovator Formulation in pH 1.2 HCl

Time(h)	% Drug release (Avg of 10 Tablets)	
	Finalized formulation	Innovator formulation
0	0	0
1	16±0.1	12±0.0
2	25±0.3	21±0.2
4	39±0.4	32±0.3
8	60±0.6	54±0.4
12	72±0.4	69±0.7
16	84±0.2	83±0.5
20	89±0.2	90±0.3
24	92±0.3	96±0.2

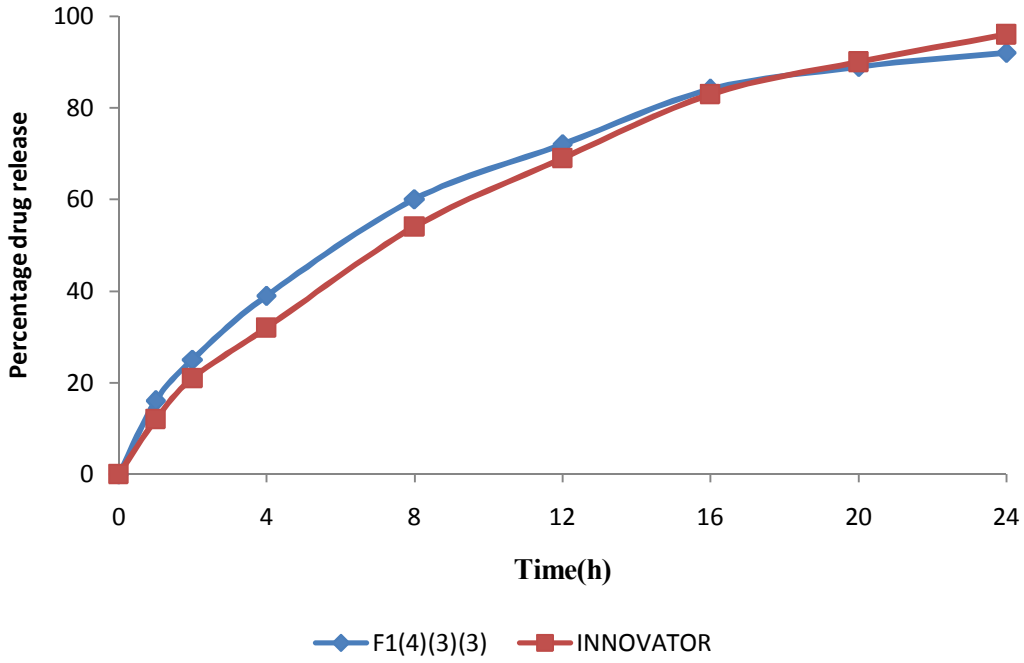


Figure.19.Comparitive dissolution profile inpH1.2 HCl

STABILITY DETAILS[57-59]

Accelerated stability study carried out as per ICH Guidelines "Q_1E, Evaluation of Stability data" (Q_1E, ICH, 2OO4) Using Stability chamber. The Optimized

formulation was selected and stability study was carried out at different condition such as refrigerator, long term and accelerated conditions for 3 months.

About 15 tablets packed in HDPE bottles and kept at above specified condition in stability chamber for three months. Tablet samples evaluated after 1st,2nd and 3rd month for drug content[58] as well as subjected for in vitro drug release study. all the parameters have not shown any much variation when compared to initial data. The dissolution[59] release profiles were analyzed with aid of dissolution similarity factor f_2 and time point analysis.

Table No: 42 Stability data

Stage	Specifications	Initial	40°c/75%RH -1M	40°c/75%RH -2M	40°c/75%RH -3M
Assay (%)	90 to 110%	98±0.1	96.3±0.2	96.1±0.3	93.9±0.2
Despropyl	0.5%	0.14±0.02	0.21±0.04	0.28±0.03	0.29±0.05
3-oxo	0.5%	0.05±0.03	0.07±0.04	0.09±0.02	0.11±0.01
N-Methyl	0.5%	0.12±0.01	0.32±0.03	0.35±0.01	0.38±0.02
N-oxide	0.5%	0.09±0.03	0.11±0.04	0.14±0.02	0.16±0.01
1hr (%)	5 to 20%	14±0.8	13±0.4	12±0.6	10±0.5
8 hr(%)	45 to 70%	55±1.2	53±0.8	52±1.0	50±0.9
24 hr(%)	NLT 80%	96±1.4	89±1.2	86±1.6	84±1.3
Physical observation		white	No change in colour	No change in colour	No change in colour

Results And Discussion

RESULTS AND DISCUSSION

Preformulation studies

The Preformulation studies done initially for pure API, confirmed that active ingredient is high soluble,90% of particle is less than 50 microns measured by Malvern sizer, flow property is less, hence need of lubricant and magnesium stearate.The results were shown in Table No:9.

Drug-Excipient Compatibility

Drug and Excipients were passed through 40mesh screen and mixed in suitable ratios and loaded in glass vials and analysed the impurity levels for Initial week and Fourth week in HPLC.

Table No: 43 Observation of Drug-Excipient compatibility

COMBINATION	ISSUES	OVERCOME
Drug + PVPK-90	Leads to increase in N-Oxide impurity when it is intimate contact with API.	PVP in our formulation is added at a stage where API is sufficiently diluted with HPMC and Lactose, hence intimate contact is avoided.
Drug +Colloidal Sio_2 Drug + Mg. Stearate	Leads to increase in 3-OXO impurity when it is intimate contact with API.	Colloidal sio_2 and Mg.stearate are added both during pre and post compaction stages, where the ingredients are not in intimate contact with API.
Drug +Opadry pink Drug+ Ethyl cellulose Drug + Tri ethyl citrate	Also found to increase upon intimate contact with API	These ingredients are coating agents where they are not in intimate contact with API, hence replacement was not found to be necessary.
Drug + Stearic acid Drug + Citric acid Drug + PEG 6000	Leads to much increase in impurity levels	These are not used because of Incompatibility, hence they are ignored

Product development

Selection of process

Since the drug is moisture and heat sensitive, we cannot proceed with wet granulation in addition to that tablets in wet granulation leads to increase in Despropyl and N-methyl Hydroxyl impurity. In Direct compression leads to increase in content and blend un uniformity, hence it is also ignored. With dry granulation Absence of impurity level and there will not content and blend un uniformity, in addition to that flow property is increased hence we selected dry granulation process in optimisation.

Formulation development

Optimization of rate controlling polymers

During this stage, optimization of polymers using Hydrophilic and Hydrophobic polymers was done.F1 and F2 shows good release over F3 and F4 because F3 and F4 are use of hydrophobic polymers, hence confirmed the use of Hydrophilic polymers (F1) in our Formulation.

Optimization of PVP K90

Release of Entrapped drug from highly viscous matrix is not easy, leading to incomplete release, hence a release modifier which modulates the rigidity of matrix is necessary for obtaining completeness of release. Among the four formulations F1 (4) gives best results and hence used in formulation.

Optimization of Sodium carboxy methylcellulose

Complete Replacement of PVPK 90 with Sodium carboxy methyl cellulose caused the dissolution profile to be slower and completeness of drug release is not achieved, hence it was decided to partially replace PVPK 90 rather than complete replacement.

Optimization of functional coating formula

Among all ratios of Ethyl cellulose and Opadry white (50:50, 40:60, 20:80) the ratio of 20:80 was found to provide the desired release profile because Ethyl cellulose is Hydrophobic it will retard the drug release with increase in concentration.

Process optimization

The results came to know that the percentage of drug release is almost same in all process. But there are no issues in dry granulation; in addition to that flow property is increased and hence finalized use of Dry granulation.

Formulation Evaluation

Evaluation of granules

The granules are evaluated for Bulk density, tapped density, Angle of repose Carr's index, Hausner ratio by following the procedures as per pharmacopoeia.The results were satisfactory and were shown in Table No: 28.

Thickness, Weight variation, Hardness and Friability

The prepared tablets were characterized for thickness, weight variation, hardness and friability by following the procedures as per pharmacopoeia, to check the stability of tablets during transportation, packaging and storage. The results obtained in all the formulations were within pharmacopoeia standards. The results were tabulated in Table No: 30.

***In-vitro* Release kinetics**

Data of *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Ropinirole from the tablet. To find out the mechanism of drug release from hydrophilic matrices, the *in-vitro* dissolution data of each formulation with different kinetic drug release equations. Namely Zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_Ht^{1/2}$ and Peppas: $F=K_mt^{n\ 60}$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 iszero order kinetic drug release constant, $K_H$is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporatinggeometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism.

Table No: 44 Diffusion characteristics of Ropinirole Extended release tablet formulations

Formulation code	Correlation coefficient values (R^2)		Diffusion exponent value (n)
	Zero Order	Higuchi's Model	
F1	0.945	0.995	0.535
F2	0.955	0.996	0.555
F3	0.975	0.993	0.560
F4	0.978	0.997	0.604
F1(1)	0.939	0.993	0.547
F1(2)	0.936	0.992	0.530
F1(3)	0.944	0.992	0.588
F1(4)	0.931	0.991	0.505
F1(4)(1)	0.969	0.997	0.628
F1(4)(2)	0.969	0.998	0.590
F1(4)(3)	0.955	0.997	0.531
F1(4)(3)(1)	0.991	0.965	0.742
F1(4)(3)(2)	0.959	0.990	0.805
F1(4)(3)(3)	0.944	0.994	0.567

Table No: 45 Diffusion exponent drug release mechanism[60]

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.45	Fickian release
2	0.45 to 0.89	Non fickian release
3	0.89	Case II transport
4	> 0.89	Super case II transport

***In-vitro* drug release study when compared with Innovator Product**

The Tablet from the finalized or optimized formula is taken and it is compared with Innovator medium (pH 4 Citrate buffer) is used and compare the dissolution profiles of our formulation and innovator formulation. The percentage of drug release is almost same to the innovator formulation, in addition to that when

compared with other dissolution medium like pH 1.2 HCl and pH 6.8 Phosphate buffer, dissolution profiles conclude that test and reference products are pharmaceutically equivalent.

Release kinetics when compared with Reference formulation

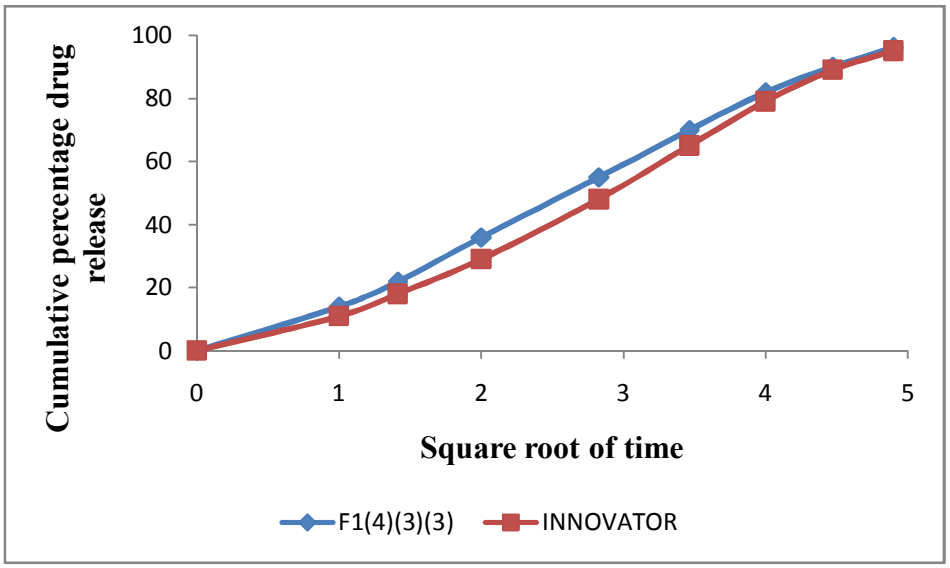


Fig.20. Higuchi plot of Finalized v/s Reference formulation

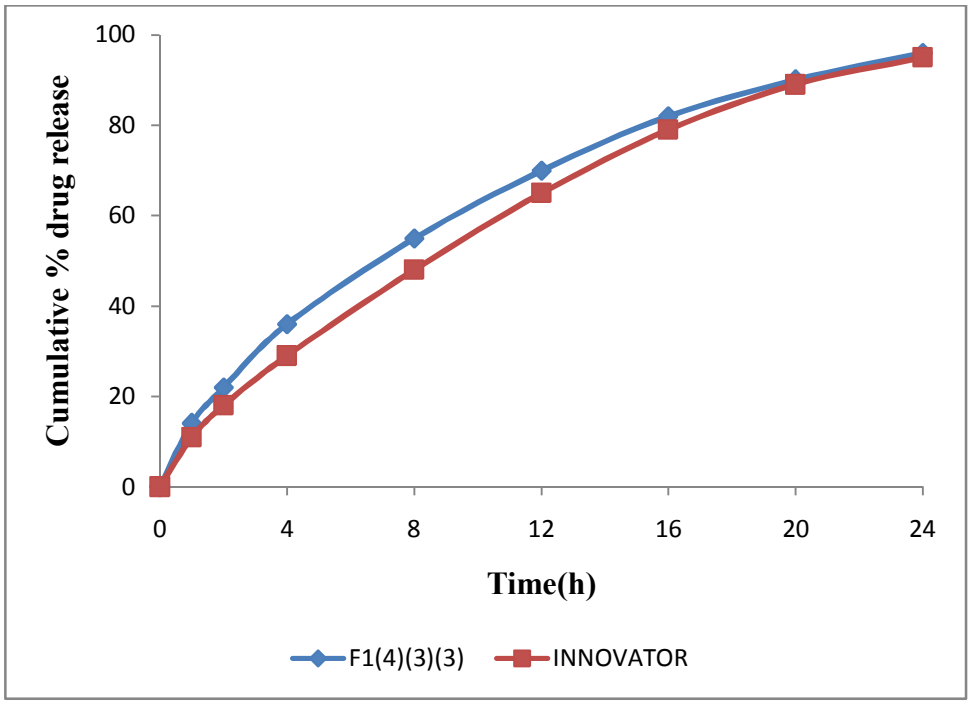


Fig.21. Zero order kinetics of Finalized v/s Reference formulation

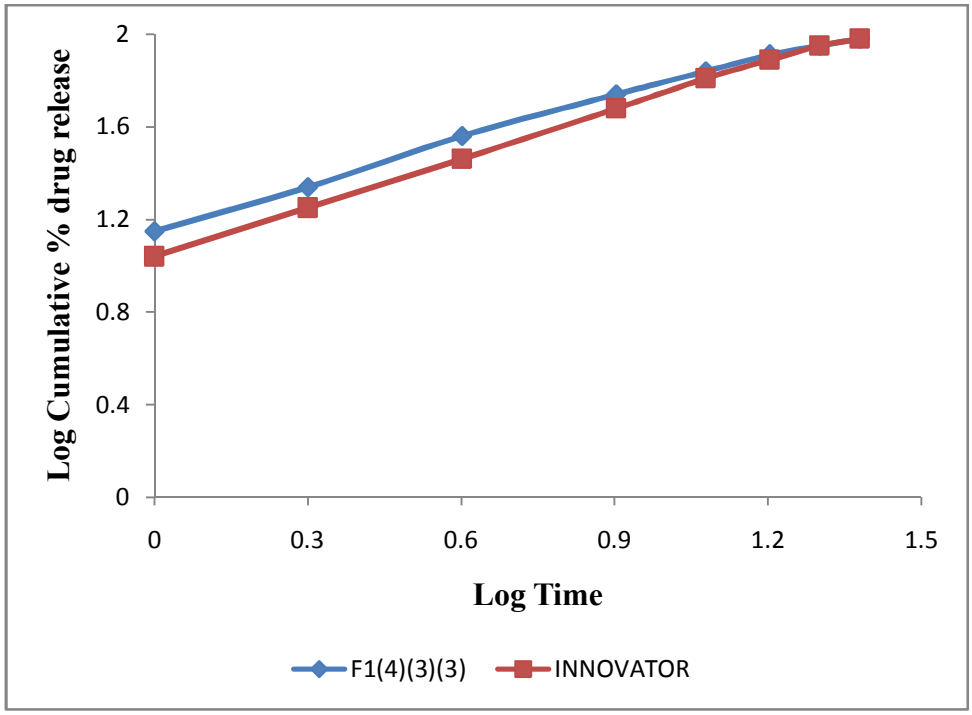


Fig.22. Peppa's plot of Finalized v/s Reference formulation

Table No: 46 Comparitive Diffusion characteristics of Finalized v/s Reference

Formulation	Correlation coefficient values (R^2)		Diffusion exponent value (n)
	Zero Order	Higuchi's Model	
Optimized formulation	0.969	0.992	0.610
Reference formulation	0.982	0.993	0.695

Concludes our Finalized and Reference formulation follows Higuchi model Non-fickian transport

Stability studies

The stability studies of Finalised formulation were carried out at accelerated condition of 40±2 ^{0}C, 75±5 % RH conditions for 3 months periodically checked at 1Month, 2 Month, and 3 Month for Impurities, Assay, and Dissolution. The results are within specification[61] are tabulated in Table No: 42.

Summary And Conclusion

SUMMARY AND CONCLUSION

Ropinirole Extended Release Tablets were Generic product of REQUIP XL(Innovator) of GlaxoSmithKline. The Preformulation studies includes drug excipient compatibility by HPLC was conducted and the results obtained showed that good compatible with Ropinirole.In the present study, the tablets were prepared by dry granulation. During the core optimization, formulation (F1(4)(3)(3)) shows better drug release over 24 hrs of time and its release is 98%, this formula is optimized for functional coating optimization, Among ratios of ethyl cellulose and Opadry white the ratio of 20:80 was found to provide the desired release profile and the tablets were evaluated for Thickness, Hardness, Friability, and Assay. From the drug release kinetics follows Higuchi model Non-fickian transport. Dissolution profile concludes that our product and innovator product are pharmaceutically equivalent. Stability studies conducted according to ICH guidelines carried out for a period of 3 months in short term period. The results were within the specification at accelerated conditions concludes our formulation is stable.

Bibilography

BIBLIOGRAPHY

1. Gilberts, Banker, Neil R. Anderson. The Sustained release dosage forms; The Theory and Practice of Industrial Pharmacy.CRC Press 1990; 4thEd: 430-456.
2. John C and Morten C. The Science of Dosage Form Design Modified release per oral dosage forms. Churchill Livingstone 2002; 2nd Ed: 290-300.
3. Joseph Robinson, Vincent L, Lee. Controlled drug delivery fundamentals and applications. Marcel Dekker Inc, 1987; 3-61.
4. Howard Ansel, Loyd V, Nicholas G. Pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins, 2004; 10th Ed: 260-275.
5. Brahma Singh, Kwon Kim. Drug delivery of Oral route, Encyclopedia of pharmaceutical technology.Inferma health care, 2010; 1(4): 1242-1261.
6. Siepmann, Lecomte, Bodmeier. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. Journal of Controlled Release, 2007; 60: 379–389
7. Sampath, Bhowmik, Shravan.Sustained Release Drug Delivery System Potential. Pharma journal,2012;1(2):48-60
8. Bechgaard G, Nelson H.controlled release multiple units and single unit doses. Drug Dev. Ind. Pharm, 2008; 3(5): 5-9.
9. Brahmankar D and Jaiswal S. Biopharmaceutic and pharmacokinetics. Vallabh Prakashan,2011, 5th Ed: 396-410
10. Ritchel WA. Biopharmaceutic and pharmacokinetic aspects in the design of controlled release per-oral drug deliver system. Drug Dev Ind Pharm, 1989; 15: 1073-103.

11. Shahrzad, Kurt, Fegely. Investigation of the Effects of Hydro alcoholic Solutions on Textural and Rheological Properties of Various Controlled Release Grades of Hypromellose. AAPS PharmSciTech, 2009; 10(1):77-80.
12. Amelia, Pralhad, Rakesh. Sustained release microspheres of ropinirole hydrochloride:Effect of process parameters. Acta Pharm, 2011;5(2):363–376.
13. Juliane Weber, Gillian. Ropinirole Prolonged Release in Advanced Parkinson's disease. Adis drug profile2009; 23 (1): 81-90.
14. Pahwa R, Stacy M, Factor S. Ropinirole 24hour Prolonged release: randomized, Controlled Study in advanced Parkinson disease. Neurology, 2007;68:1108-15.
15. Goolea J, Pilcer G. Pharmaco scintigraphic and pharmacokinetic evaluation on healthy human volunteers of sustained-release floating minitablets containing levodopa and carbidopa. International Journal of Pharmaceutics, 2008; 364: 54–63.
16. Ranjith, Vamsi, Sandeep. Factors Influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms. International Journal of Pharmaceutical Sciences and Nanotechnology 2009; 2(3): 583-594.
17. Peter A. Levodopa therapeutics for Parkinson's disease. Parkinsonism and Related Disorders, 2009; Supplement1:15-21.
18. Neha Singh, Viness Pillay. Advances in the treatment of Parkinson's disease. Progress inNeurobiology, 2007; 81:29–44.
19. Vincenzo, Giuseppe. Selective Catechol-O-Methyl transferase Inhibitors as Therapeutic Agents in Parkinsonism Disease, 2003; 81(1):1-36.

20. Adnan Azeema, Sushama, Negi. Oil based nanocarrier system for transdermal delivery of ropinirole. International Journal of Pharmaceutics, 2012; 42: 436-444.
21. Lauren C, Robert A. Optimizing bioavailability in the treatment of Parkinson's disease. Neuropharmacology, 2007; 53(2): 791-800.
22. Deepak Sahu, Rana. Formulation development of Quetiapine Fumarate SR matrix Tablets, Der Pharmacia Sinica, 2010; 1(1): 48-57.
23. Wakode R**,** Bajaj A. Formulation and development of once a daily sustained release matrix tablet for pramipexole. International Journal of Pharmaceutics and Cosmetology, 2010; 1(5): 241-245.
24. Raghavendra R, Gandhi S. Formulation and evaluation of sustained release matrix tablets of tramadol hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences, 2009;1(1):25-29.
25. Yucheng Sheng, Yingchun. Systematic Evaluation of Dose Proportionality Studies in Clinical Pharmacokinetics, Current Drug Metabolism, 2010; 11(3): 526-537.
26. Eytan A, Klausner, Eran Lavy. Novel levodopa gastro retentive dosage form: in-vivo evaluation in dogs. Journal of Controlled Release, 2003; 48: 117-126.
27. http://Requip®XL™ Prescribing Information.com
28. Rivest J, Quinn N, Marsden. Dystonia in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Neurology, 2004; 157-160
29. Schapira, Stocchi F, Hunter. Comparison of adjunctive ropinirole prolonged release and ropinirole immediate release in patients with advanced

Parkinson's disease: a posthoc perprotocol analysis of the prepared study. Mood Disord, 2008; 23-26.

30. De Vane, Schwartzberg A, Nemeroff. Principles of pharmacokinetics and pharmacodynamics, American Psychiatric Press Textbook of Psychopharmacology.J Clin Psychiatry, 2008; 3: 14-19
31. Rowe RC. The molecular weight and molecular weight distribution of hydroxyl propyl methylcellulose used in the film coating of tablets. J Pharm Pharmacol, 1980; 32: 116–119.
32. Banker G, Peck G, Jan S, Pirakitikulr P. Evaluation of hydroxyl propyl cellulose and hydroxyl propyl methyl cellulose as aqueous based film coatings. Drug Dev Ind Pharm,1981; 7: 693–716.
33. Sako K, Sawada T, Nakashima H. Influence of water soluble fillers in hydroxyl propyl methyl cellulose matrices on in vitro and in vivo drug release. J Control Release 2002; 81: 165–172.
34. Khan A, Rhodes C. Evaluation of different viscosity grades of sodium carboxy methylcellulose as tablet disintegrants. Pharm Acta Helv 2005; 50: 99–102.
35. Shah N, Lazarus J, Jarwoski C. Carboxy methylcellulose: Effect of degree of polymerization and substitution on tablet disintegration and dissolution. J Pharm Sci, 2001; 70 (6):611-613.
36. Christensen M, Johansen P, Hau C. Storage of polyvinylpyrrolidone (PVP) in tissues following long-term treatment with a PVP containing vasopressin preparation. Acta Med Scand. 1998; 204: 295–298.
37. Ozturk G, Palsson B.Mechanism of release from pellets coated with an ethyl cellulose-based film. J Control Release, 2000; 14(3): 203–213.

38. Colombo P, Conte U, Gazzaniga A, Maggi L. La Manna A. Drug release modulation by physical restrictions of matrix swelling, Int. J. Pharm. 1990; 63: 43-48.

39. Schwartz, Lieberman, Lachman. Preformulation testing in Pharmaceutical Dosage forms Tablets. CBS Publication, 1986; 3rded: 57-68.

40. Sahasrabuddhey B, Nautiyal R, Acharya H.Isolation and characterization of some potential impurities in Ropinirole hydrochloride. J.Pharm.Bio.med Anal, 2007; 43: 1587-1593.

41. Sreekanth N, Babu rao, Mukkanti K.RP-HPLC method development and validation of ropinirole hydrochloride in bulk and pharmaceutical dosage forms. Ijpps,2009; Vol-1:186-192

42. Martins M, Farinha made comparative study of methods and specifications in Uniformity of dosage units. Eur. Pharm.3rd and USP 23 J. Pharm. Biomed. Anal, 2005; 18:487-495.

43. http://www.USFDA/Guidance for industry/Extended release dosage forms.htm

44. Pilgaonkar, Rustomjee, Gandhi. Development of an Extended Release Formulation of Ropinirole hydrochloride Using RubiSRT Technology in Rubicon Research Private Limited, AAPS PharmaSci tech, 2009; 10:30-32.

45. Kiil.Drug delivery from swellable hydroxyl propyl methyl cellulose matrices: model-based analysis of observed radial front movements. J. Control. Release 2003, 90: 1–21.

46. Ford J, Rubinstein H, McCaul F, explained the Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxyl propyl methylcellulose Matrix tablets. Int J Pharm, 2005; 40: 223-234.

47. K.Raghuram, Srinivas. Formulation and Invitro Evaluation once daily sustained release matrix tablets of Nicorandil. AAPS PharmSciTech, 2003; 12:10-14.

48. Tiwari, Murthy, Pai M. formulated Controlled release of Propranolol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharm Sci Tech 2003; 4 (3): 12-17.

49. Dinanath Gaikwad, Jadhav, Amol Limkar.Sustained Release Tablet of Aceclofenac by Film Coating in Ijps,2006;vol 2:42-44.

50. Huang, Yi-Hung Tsai, Wan-Chiech Yang. Once-daily propranolol extended-release tablet dosage form: formulation design and In vitro/ In vivo investigation.Eur J Pharm Biopharm, 2005; 58: 607-614.

51. Holgado M, Iruin A, Alvarez. Invitro evaluation of a controlled release formulation to produce wide dose interval morphine tablets. Eur J Pharm and Bio pharmaceutics, 2008; 70:544-549.

52. Susheel, Malathi S, Ravi T. Analysis of Ropinirole in tablet dosage form. Ind J Pharm Sci, 2007; 69:589-590.

53. Rahman,Sayeed Hasan, Sumon Roy. Formulation and evaluation of Ranolazine sustained release matrix tablets using Eudragit and HPMC. Int J Pharm Biomed Res, 2011; 2(1): 7-12

54. Higuchi T. Mechanism of rate of sustained action medication. J Pharm. Sci, 52: 1145-1149 (1985).

55. Korsmeyer, Gurny W, Doelker. Mechanisms of solute release from porous hydrophilic Polymers. Int J Pharm, 1983; 15: 25-35.

56. Shah V, Tsong, Sathe, In vitro dissolution profile comparison - statistics and analysis of the similarity factor f2. Pharm Res, 1998; 15: 889-896.

57. Azeem, Farhan, Ahmad. Development and validation of a stability-indicating method for determination of ropinirole in the bulk drug and in pharmaceutical dosage forms. Acta Chromatogr, 2008;20: 95–107.

58. Thoppil S, Cardoza, Amin. Stability indicating HPTLC determination of Trimetazidine as bulk drug and in pharmaceutical formulations. J Pharm Biomed, 2001; 25(1):15–20.

59. Sanjay, Singla, Neha.Stability Testing of Pharmaceutical Products.Journal of Applied Pharmaceutical Science, 2012: 02 (03): 129-138.

60. Schwarz, Kibbe. Drug release from wax matrix analysis of data of order of Kinetic Release and diffusion controlled model. J Pharm Sci 1998; 57: 274-277.

61. European Medicines Agency – Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99), 12 -13.